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Initial Report of the TSCA Interagency Testing Committee and Information Dossiers on Substances Designated

TSCA Interagency Testing Committee, Washington, D C

Prepared for

National Science Foundation, Washington, D C

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INITIAL REPORT OF THE TSCA INTERAGENCY TESTING COMMITTEE
TO THE
ADMINISTRATOR, ENVIRONMENTAL PROTECTION AGENCY

October 1, 1977

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CONTENTS

Committee Membership i(c)
Acknowledgments ii
SUMMARY iii

CHAPTER 1. INTRODUCTION

1.1 Background 1
1.2 Committee Establishment and Responsibilities 2

CHAPTER 2. DEVELOPMENT OF THE COMMITTEE'S INITIAL RECOMMENDATIONS

2.1 Selection of the Committee's Basic Approach 4
2.2 Establishment of the Initial Listing 7
2.3 Reduction to the Master File 7
2.4 Selection of the Preliminary List 8
2.5 Public Comment on the Preliminary List 10
2.6 Selection of Substances for Detailed Review 11
2.7 Consideration for Listing and Designation 14
2.8 Consideration of Availability of Testing Facilities and Personnel 15

CHAPTER 3. RECOMMENDATIONS OF THE COMMITTEE

3.1 Substances and Categories of Substances Recommended for Testing 17
3.2 Reasons for Recommending Testing of the Substances and Categories 19
3.2.A Alkyl Epoxides 19
3.2.B Alkyl Phthalates 20
3.2.C Chlorinated Benzenes, Mono- and Di- 21
3.2.D Chlorinated Paraffins, 35-64% Chlorine 22
3.2.E Chloromethane 23
3.2.F Cresols 24
3.2.G Hexachloro-1,3-Butadiene 25
3.2.H Nitrobenzene 26
3.2.I Toluene 27
3.2.J Xylenes 28

APPENDICES

APPENDIX A DATA SOURCES USED FOR PREPARATION OF THE INITIAL LIST 29
APPENDIX B PRODUCTION, RELEASE AND EXPOSURE SCORES 32
APPENDIX C ORDERING OF THE CHEMICALS BASED ON PRODUCTION, RELEASE, AND EXPOSURE 38
APPENDIX D BIOLOGICAL AND ENVIRONMENTAL SCORES 39

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EXECUTIVE OFFICE OF THE PRESIDENT
COUNCIL ON ENVIRONMENTAL QUALITY
722 JACKSON PLACE, N. W.
WASHINGTON, D. C. 20006

October 4, 1977

Honorable Douglas M. Costle
Administrator
Environmental Protection Agency
Washington, D.C. 20460

Dear Mr. Costle:

The enclosed document is the first official report submitted to you by the Interagency Testing Committee pursuant to Section 4(e) of the Toxic Substances Control Act (TSCA). It reflects the consensus of representatives from all eight member agencies: that the ten listed substances and categories of substances be recommended as high priority for testing under TSCA and designated for consideration by EPA within twelve months.

The report describes the process employed by the Committee in making its recommendations and the rationale for each designation. A supporting dossier for each designation will be forwarded to the Office of Toxic Substances in the next few weeks.

Only a portion of the compounds identified in the July preliminary report has been considered to date. The first revision of our recommendations will be based largely upon further review of those chemicals previously identified. Because this is a continuing process, we will, of course, identify additional chemicals for such review as information becomes available to us.

The Committee has been hampered in its deliberations by the lack of a readily available and consolidated source of data on the many chemicals to which man and the environment are exposed. Other activities under TSCA, e.g., development of coordinated data systems, inventory reporting, and other information collection under Section 8, should be of considerable value in future Committee efforts. Therefore, we expect that a number of additional substances will be listed and integrated in our future reports.

We hope our analysis and recommendations will be helpful to EPA in its implementation of the Toxic Substances Control Act.

Sincerely,

Warren R Muir

Warren R. Muir, Ph.D.
Chairman
TSCA Interagency Testing
Committee

TSCA INTERAGENCY TESTING COMMITTEE

Statutory Member Agencies

Council on Environmental Quality

Warren R. Muir, Member and Committee Chairman

Department of Commerce

Sidney R. Galler, Member

Bernard Greifer, Alternate

Environmental Protection Agency

William M. Upholt, Member

James R. Beall, Alternate

National Science Foundation

Marvin E. Stephenson, Member and Committee Vice Chairman

Carter Schuth, Alternate

National Institute of Environmental Health Sciences

Hans L. Falk, Member

Warren T. Piver, Alternate

National Institute for Occupational Safety and Health

Norbert P. Page, Member

Jean G. French, Alternate

National Cancer Institute

James M. Sontag, Member

Occupational Safety and Health Administration

Grover C. Wrenn, Member

James M. Vail, Alternate

Liaison Agencies (non-Voting)

Department of Defense

Seymour L. Friess

Food and Drug Administration

Allen H. Heim

Department of Interior

Charles R. Walker

U.S. Consumer Product Safety Commission

Robert M. Hehir

Joseph McLaughlin

Committee Staff

Secretary: Phyllis D. Tucker

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-- EPA staff members who assisted the Committee in a variety of activities, and particularly:
Donald Barnes, Office of Toxic Substances
Joyce Dain, Interim Secretary to the Committee
John Lyon, Office of General Counsel
Joseph Merenda, staff support to EPA member
Lamar Miller, interim staff support to EPA member
Ralph Northrop, Jr., Office of Toxic Substances

-- the numerous experts who prepared presentations and materials for the Committee; and

-- the many individuals and organizations who submitted comments on the Committee's Preliminary List.

SUMMARY

The Toxic Substances Control Act (TSCA) established the TSCA Interagency Testing Committee, giving it the continuing responsibility to identify and recommend to the Administrator of the Environmental Protection Agency chemical substances and mixtures which should be tested to determine their hazards to human health and the environment. The Committee's initial recommendations are to be published in the Federal Register and transmitted to the EPA Administrator within nine months of the effective date of TSCA. The Committee is to consider additions to its recommendations at least every six months.

In meeting its charge, the Committee has, with the assistance of a technical support contractor, carried out a multi-step screening procedure to identify for its detailed review a limited number of substances and categories of substances likely to have priority for testing to determine their effects on human health and the environment. A number of substances and categories identified by this process have been reviewed by the Committee, which has given careful consideration to each of the eight factors specified in Section 4(e)(1)(A) of TSCA. The Committee has also considered such factors as test programs currently in progress, the current status of regulatory action with respect to a substance, and the need for test data on all members of certain categories rather than on one or more individual members of the category.

In July, 1977, the Committee published a Preliminary List of 330 substances and categories of substances along with a background document describing the methods used by the Committee in making those selections. The Preliminary List included substances and categories selected primarily on the basis of potential for human exposure and environmental release. Public comments received on the Preliminary List were reviewed by the Committee and considered in the development of the Committee's initial recommendations.

Subsequently, the chemicals on the Preliminary List and chemicals added to the Preliminary List based on the public comments were further screened by the Committee based primarily on their potential for adverse human and/or environmental effects, but also continuing to consider their exposure potential. Available data on and potential for carcinogenic, mutagenic, teratogenic and chronic toxic effects, as well as their ability to bioaccumulate or cause deleterious environmental effects were considered. A scoring system which took into account both available information and the lack of it for these factors was used in this process. Using these scoring results and its scientific judgment, the Commmittee further narrowed the list under consideration to about 80 substances and categories. Aided by information dossiers prepared by its contractor, the Committee reviewed about half of these compounds and has selected for inclusion in its initial recommendations to the EPA Administrator four individual substances and six categories of substances. Each is being

designated by the Committee for consideration by EPA within the next 12 months. They are (arranged alphabetically):

Substance or Category	Testing Recommended
Alkyl Epoxides	Carcinogenicity, mutagenicity, teratogenicity, other chronic effects, environmental effects, and epidemiological study
Alkyl Phthalates	Environmental effects
Chlorinated Benzenes, Mono- and Di-	Carcinogenicity, mutagenicity, teratogenicity, other chronic effects, environmental effects, and epidemiological study
Chlorinated Paraffins	Carcinogenicity, mutagenicity, teratogenicity, other chronic effects, and environmental effects
Chloromethane	Carcinogenicity, mutagenicity, teratogenicity, and other chronic effects
Cresols	Carcinogenicity, mutagenicity, teratogenicity, other chronic effects, and environmental effects
Hexachloro-1,3-butadiene	Environmental effects
Nitrobenzene	Carcinogenicity, mutagenicity, and environmental effects
Toluene	Carcinogenicity, teratogenicity, other chronic effects, and epidemiological study
Xylenes	Mutagenicity, teratogenicity, and epidemiological study

The Committee's reasons for each recommendation and a more detailed definition of each of the categories are presented in Section 3.2. The Committee expects that the precise definition of each category will be considered further by EPA in the course of developing testing rules. The Committee also recognizes that certain members of a category may already have been adequately tested for one or more of the effects for which testing of the category has been recommended. In that case, no further testing for that combination of substance and effect would be needed.

A dossier summarizing the information considered by the Committee in selecting each substance or category will be forwarded to EPA in the next few weeks. The Committee will continue its review of the remaining substances and categories already selected for detailed review, and may identify and review others, in anticipation of its next report.

INITIAL REPORT OF THE TSCA INTERAGENCY TESTING COMMITTEE
TO THE
ADMINISTRATOR, ENVIRONMENTAL PROTECTION AGENCY

October 1, 1977

CHAPTER 1. INTRODUCTION

1.1 BACKGROUND

Section 4(e) of the Toxic Substances Control Act (P.L. 94-469, hereafter referred to as TSCA) established the TSCA Interagency Testing Committee. That Committee has the continuing responsibility to identify and recommend to the Administrator of the Environmental Protection Agency chemical substances or mixtures which should be tested to determine their hazard to human health or the environment. The statute provides that the Committee shall make its initial recommendations to EPA by October 1, 1977.

To carry out this responsibility, the Committee has developed and executed a multi-step screening procedure to identify for its detailed review a number of chemical substances and categories of chemical substances expected to have a high priority for testing based on the criteria set forth in Section 4(e)(1)(A) of TSCA. The Committee received extensive technical support in this screening, and in the gathering of data on substances and categories selected for detailed review, from Clement Associates, Inc. under a contract with the National Science Foundation. After reviewing the information available to it on each candidate, including public comments submitted in response to the Committee's July, 1977, publication of a preliminary list of substances under consideration, the Committee has selected the ten substances and categories being recommended to the EPA Administrator in this report. As required by the statute, the Committee will continue its review process, reporting to the EPA Administrator within six months from the date of this report such additional recommendations as the Committee finds desirable during that period.

This report documents the procedures used by the Committee in selecting those substances and categories now being recommended for testing, and, as required by the statute, provides the Committee's reasons for making each such recommendation. In addition to the material contained in this report, the Committee is now finalizing a series of dossiers developed by its technical support contractor which will summarize all of the non-confidential information considered by the Committee in deciding to recommend each substance or category for testing. These dossiers will be transmitted to the EPA in a few weeks.

1.2 COMMITTEE ESTABLISHMENT AND RESPONSIBILITIES

The Committee, as established by Section 4(e) of TSCA, has eight members, appointed by the eight Federal agencies identified for membership in Section 4(e)(2)(A) of the Act. In addition, a number of alternates have been designated as permitted by Section 4(e)(2)(B)(i). The Committee has adopted the name "TSCA Interagency Testing Committee", which is frequently shortened in this report to "Committee". As provided by Section 4(e)(2)(B)(iii), it has selected a chairman from among its members. The Committee has also invited several other Federal agencies with programs related to the control of toxic substances, but which were not included in the statutory membership of the Committee, to designate liaison representatives to attend Committee meetings. Current Committee members, alternates, and liaison representatives are identified in the frontispiece.

The Committee's testing priority recommendations are required by Section 4(e) to be published in the Federal Register and transmitted to the EPA Administrator within nine months of the January 1, 1977, effective date of TSCA. At least every six months thereafter, the Committee is required to review its recommendations and make such revisions as are necessary.

The Committee's recommendations are to be in the form of a list of chemical substances or mixtures set forth, either individually or in groups, in the order in which the Committee determines the EPA Administrator should consider taking action under Section 4(a) in developing and promulgating testing regulations. The Committee is authorized to designate up to 50 of these substances or groups for which the EPA Administrator must within 12 months either initiate rulemaking requiring their testing or publish reasons for not taking such action.

In developing its recommendations, the Committee is directed by Section 4(e)(1)(A) of TSCA to consider, along with all other relevant factors: the production volume, environmental release, occupational exposure, and non-occupational human exposure to the substance or mixture; the similarity of the substance or mixture in question to others known to present unreasonable risk of injury to health or the environment; the extent of data on the effects of the substance or mixture in question on health or the environment and the extent to which additional testing of the substance or mixture may produce data from which effects can reasonably be determined or predicted; and the reasonably foreseeable availability of facilities and personnel for performing the testing being recommended. The Committee is also directed by Section 4(e) to give priority attention in establishing its list of recommendations to substances or mixtures which are known or suspected to cause or contribute to cancer, gene mutations, or birth defects.

The Committee's specific reasons for including each substance or mixture in its recommendations are required to be published in the Federal Register and transmitted to the EPA Administrator along with the priority list.

While Section 4(e) refers to the Committee's recommendations as a list of "chemical substances and mixtures", Section 26(c)(1) authorizes the EPA Administrator to take actions (including the promulgation of Section 4(a) testing regulations) with respect to categories of chemical substances or mixtures as well. A category is defined in TSCA as a group whose members are similar in molecular structure; in physical, chemical, or biological properties; in use; in mode of entrance into the human body or into the environment; or in any other way, so long as the grouping is not based solely on its members being "new chemical substances" as defined in the Act. Since the EPA Administrator is authorized to promulgate testing regulations for categories of chemical substances or mixtures, the Committee has concluded that its recommendations to the EPA Administrator may also include categories (or groups) of chemical substances or mixtures, as well as individual substances and mixtures. This conclusion is consistent with Section 4(e) which states that the Committee's recommendations for testing "shall be in the form of a list of chemical substances and mixtures which shall be set forth, either by individual substance or mixture or by groups of substances or mixtures... ."

In order to maintain consistency in this report and in keeping with its meaning in TSCA, the term "category" will be used to reflect groupings of substances. "Substance" will be used to refer to both individual chemicals as well as mixtures.

CHAPTER 2. DEVELOPMENT OF THE COMMITTEE'S INITIAL RECOMMENDATIONS

2.1 SELECTION OF THE COMMITTEE'S BASIC APPROACH

Estimates of the number of chemical substances and mixtures subject to TSCA range from tens of thousands to over 100,000; the number and identities of these substances and mixtures will not be established until after the completion of the chemical inventory under Section 8(b) of TSCA. Nevertheless, all of these substances and mixtures, together with others which may be manufactured in the future, are subject to the promulgation of testing rules under Section 4(a) and are thus within the purview of the Interagency Testing Committee.

At the same time, Section 4(e) of TSCA specifies a number of factors which the Committee is to consider in determining whether to recommend a substance for testing. Careful consideration of these factors requires the collection and review of a substantial amount of data concerning the production, use, chemical and biological activity, and previous testing of each substance or category of substances under consideration.

As a result, because of the lack of a comprehensive and readily accessible data base on current chemicals, the large number of potential candidates for the Committee's consideration, and the statutory deadline for the Committee's initial recommendations to EPA, the Committee has had to select for its detailed consideration only a small subset of the possible candidates.

In considering alternative approaches to selecting a limited number of substances for detailed review, the Committee met with a number of experts on chemical data systems and chemical characterization. Several possible approaches were identified. One was a nomination approach in which Committee members or other experts would nominate specific chemicals for consideration. Another was to use structure-activity relationships to identify for review substances chemically similar to others of known hazard. Yet another approach was to focus the Committee's attention on those substances known to have high levels of production volume, environmental release, or human exposure.

After considering these alternatives, the Committee decided to adopt a combined strategy employing features of each. This resulted in a multi-step screening process wherein a relatively large number of substances were considered initially and at each subsequent step a smaller subset was selected for collection of more data and more intensive review.

The basic steps in the process adopted by the Committee, which are illustrated in Figure 1 and are described in more detail in subsequent sections, were as follows:

a. Establishment of an INITIAL LISTING of about 3,650 substances and categories of substances previously identified as potential hazards to human health or the environment,

b. Compilation of a smaller MASTER FILE (about 1,700 substances and categories) through elimination from the INITIAL LISTING of substances not in commercial production or used predominantly as pesticides, food additives, or drugs,

c. Selection of a PRELIMINARY LIST of about 330 substances and categories for further consideration based on evaluation of the production volume, environmental release, occupational exposure, and general human exposure levels of the substances in the MASTER FILE,

d. Selection of about 80 substances and categories for detailed review based on evaluation of the potential biological activity and need for health and ecological effects testing of substances appearing on the PRELIMINARY LIST,

e. Selection of substances and categories recommended for testing after review of preliminary dossiers prepared by the Committee's contractor, public comments on the PRELIMINARY LIST, and other pertinent information available to the Committee from various agencies,

f. Documentation of the Committee's reasons for including each substance or category in its list of recommendations and completion of a final dossier summarizing the information considered by the Committee in reaching its decision.

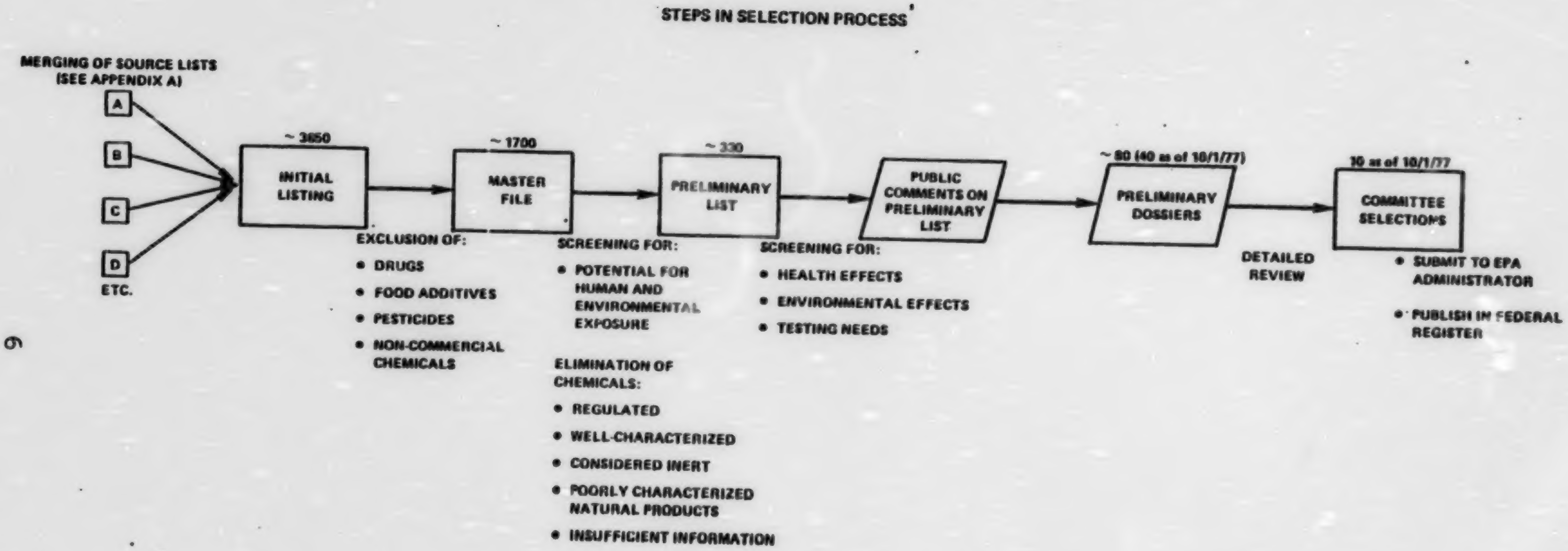
STEPS IN SELECTION PROCESS
MERGING OF SOURCE LISTS (SEE APPENDIX A)
A
B
C
D
ETC.
~ 3650
INITIAL LISTING
EXCLUSION OF:
• DRUGS
• FOOD ADDITIVES
• PESTICIDES
• NON-COMMERCIAL CHEMICALS
~ 1700
MASTER FILE
SCREENING FOR:
• POTENTIAL FOR HUMAN AND ENVIRONMENTAL EXPOSURE
ELIMINATION OF CHEMICALS:
• REGULATED
• WELL-CHARACTERIZED
• CONSIDERED INERT
• POORLY CHARACTERIZED NATURAL PRODUCTS
• INSUFFICIENT INFORMATION
~ 330
PRELIMINARY LIST
SCREENING FOR:
• HEALTH EFFECTS
• ENVIRONMENTAL EFFECTS
• TESTING NEEDS
PUBLIC COMMENTS ON PRELIMINARY LIST
~ 80 (40 as of 10/1/77)
PRELIMINARY DOSSIERS
DETAILED REVIEW
10 as of 10/1/77
COMMITTEE SELECTIONS
• SUBMIT TO EPA ADMINISTRATOR
• PUBLISH IN FEDERAL REGISTER

FIGURE 1. SELECTION SCHEME USED BY THE TSCA INTERAGENCY COMMITTEE IN SELECTING ITS INITIAL RECOMMENDATIONS TO THE EPA ADMINISTRATOR (OCTOBER 1977)

Carrying out this multi-step process required the collection, review, coding, and analysis of data on a large number of chemical substances, as well as the application of scientific judgment in many areas where adequate data were unavailable. The Committee was supported extensively in these efforts by Clement Associates, Inc. under a contract with the National Science Foundation (Contract No. NSF ENV77-15417 with partial funding by the NIEHS and NCI. The contractor employed expert consultants from a variety of disciplines in carrying out its tasks under the contract. In addition, many U.S. Government agencies made data and expertise of their employees available to the Committee for these efforts.

Several of the steps of the Committee's procedure employed quantitative scoring of the substances under consideration. Members of the Committee used their professional expertise and judgment in applying these scores to the decisions at each step.

2.2 ESTABLISHMENT OF THE INITIAL LISTING

In order to focus its initial attention on substances likely to require health and/or ecological effects testing, and for which sufficient preliminary data were likely to be available to permit more detailed reviews at later steps, the Committee chose to limit its initial consideration to substances or categories of substances which had already been identified in previous reviews as being of concern because of potential adverse effects on human health or the environment or as having large production volumes and a potential for substantial human exposure or environmental release. Nineteen separate source lists of this type were identified by the Committee and pooled to produce the INITIAL LISTING of about 3,650 substances, mixtures, and categories. The individual source lists are identified and described briefly in Appendix A.

2.3 REDUCTION TO THE MASTER FILE

The INITIAL LISTING included a number of substances having pesticide, food additive, or drug uses, all of which are regulated under other Federal statutes and are exempted from regulation by TSCA. To identify them, the INITIAL LISTING was compared with lists of pesticides prepared by the EPA and lists of food additives and drugs prepared by the Food and Drug Administration, using Chemical Abstracts Service (CAS) Registry Numbers. This initial purge of substances subject to other statutes was incomplete, since some entries on source lists did not include CAS numbers. To compensate for this, a further manual purging was required. Consideration was also given to the fact that a substance used as a pesticide, food additive or drug may also have other uses that are subject to the authority of TSCA. Since pesticides, food additives, and drugs are generally produced in limited volumes, substances identified as such but having annual production over 10 million pounds were considered likely to have other uses as well and were retained on the truncated list for further review of their uses. Substances identified as pesticides, food additives, or drugs but known to the Committee or its contractor to have other uses within the jurisdiction of TSCA were also retained.

The resulting file was reduced further by the elimination of chemicals which were judged not likely to be in commercial production. This was accomplished by comparing the file against EPA's Candidate List of Chemical Substances, prepared by the Office of Toxic Substances (dated April 1977). Again, the basis of comparison for this purge was an assigned CAS number. Consequently, this purge did not affect those chemicals on source lists for which no CAS number was given. In an attempt to eliminate substances which are not in commercial production, the following rule was adopted: any substance not identified by a CAS number which appeared on the NIOSH Registry (Source List 13 of Appendix A) and on none of the other source lists was judged not likely to be in commercial production. This decision was based on the fact that the NIOSH Registry lists any substance for which toxic effects have been reported, including research chemicals. A scan of the substances eliminated by the application of this rule demonstrated its usefulness: few of the purged substances were recognized to be in commercial production.

As a result of the purges described above, a MASTER FILE of approximately 1700 substances emerged.

2.4 SELECTION OF THE PRELIMINARY LIST

Having developed a MASTER FILE of substances to be considered for possible recommendation to EPA for testing, the Committee began to apply the eight factors explicitly identified for its consideration in Section 4(e)(1)(A). While recognizing that there would be advantages to applying all of the first seven factors* simultaneously in evaluating the relative priorities for detailed review of the substances under consideration, the Committee concluded that assembling and evaluating the necessary data for all substances on the MASTER FILE would not be feasible within the time schedule established by statute, considering the limitations of current chemical information systems and the number of professional judgments which would have to be made. Evaluation of the fifth, sixth, and seventh factors (relating to chemical similarity to substances of known hazard, existing health and environmental effects data, and need for testing) was anticipated to require more independent review and judgment and to be the more time-consuming portion of the task. Hence, the Committee decided to further reduce the number of substances under consideration before explicitly evaluating those factors which had, to some extent, already been reflected in the choice of source lists.

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* The eighth factor, the reasonably forseeable availability of facilities and personnel for performing the needed testing, was considered principally by the Committee in terms of the aggregate facilities and personnel needs for carrying out all of the Committee's recommendations. See Section 2.8 for further discussion of this factor.

This reduction, which resulted in the selection of the PRELIMINARY LIST, was based principally on evaluation of the first four factors identified for the Committee's consideration in Section 4(e)(1)(A) of TSCA. These are:

(i) quantity of the substance produced annually

(ii) amount of the substance released into the environment

(iii) number of individuals occupationally exposed and duration of their exposure

(iv) extent to which the general population will be exposed.

Using a combination of published data and judgment, the Committee's contractor made an attempt to score each substance in the MASTER FILE for these four factors. Appendix B describes in more detail how scores were assigned to substances. Information on the use or uses of a substance was critical to the assignment of scores for environmental release and general population exposure, and scores for those factors could not be assigned if use information could not be found by the contractor. For about 1,000 of the 1,700 substances in the MASTER FILE this was the case; as a result, for only about 700 of the substances was it possible to assign scores. By combining the scores for the four factors, as described in Appendix C, a rank-ordered list of the scored substances was prepared for the Committee's consideration.

In selecting the approximately 330 substances and categories included on the PRELIMINARY LIST, the Committee considered all of the scored substances and eliminated from current consideration a number of them which in the Committee's professional judgment were found to be:

a. Currently under stringent regulation or of lower priority for the Committee's purposes because their hazard is reasonably well characterized (e.g., vinyl chloride and mercury);

b. Essentially inert materials (e.g. certain polymers) or substances reasonably well characterized as having low toxicity (e.g., methane);

c. Covered by testing requirements under food, drug and cosmetic or pesticide legislation (e.g., citric acid); or

d. Certain natural products (e.g., asphalt) whose consideration should be deferred pending better characterization for testing purposes.

Others of the scored substances were specifically selected by the Committee for inclusion on the PRELIMINARY LIST based on judgment of members that further review was needed. The remainder of the scored substances were considered for inclusion on the PRELIMINARY LIST based on their relative ranking in the scoring process.

In addition to the scored substances, the Committee also considered in selecting the PRELIMINARY LIST the unscored substances from the MASTER FILE and a limited number of additional substances recommended by Committee members or the Committee's contractor. A number of substances from these sources were included on the PRELIMINARY LIST based on the Committee's knowledge of the substance and its uses or the Committee's professional judgment that the substance should be further evaluated.

In reviewing substances for possible inclusion on the PRELIMINARY LIST, the Committee also considered the desirability of grouping substances into categories. In several cases the Committee grouped chemically-related substances from the MASTER FILE while in other cases the Committee retained groups which had already appeared in one of the source lists. About 15% of the entries on the PRELIMINARY LIST were categories.

2.5 PUBLIC COMMENT ON THE PRELIMINARY LIST

The PRELIMINARY LIST, together with a background document describing its development, was published by the Committee in July, 1977. Notice was published by the Committee in the Federal Register (42 FR 30531 and 42 FR 40756) announcing the availability of the list and background document and requesting public comment. Comments were specifically requested on:

a. The methodology used by the Committee in developing the PRELIMINARY LIST;

b. Substances not appearing on the PRELIMINARY LIST which commentors might recommend for consideration by the Committee and the commentor's reasons for the recommendation;

c. Substances appearing on the PRELIMINARY LIST which commentors might recommend that the Committee not consider further and the reasons for that recommendation; and

d. Comments on the needs for and relative priority of testing of the substances being considered by the Committee.

As an additional aid to commentors and others interested in the Committee's activities, copies of the list of substances comprising the MASTER FILE and a tabulation of the scores for production volume, environmental release, and occupational and general population exposure considered by the Committee in selecting the PRELIMINARY LIST were made available for public inspection at the headquarters and regional offices of the Environmental Protection Agency.

Comments on the PRELIMINARY LIST were received from about 65 industrial firms, trade associations, environmental organizations, government agencies, and individuals. About two-thirds of the commentors recommended deletion from the Committee's further consideration of one or more substances or categories appearing on the PRELIMINARY LIST, while four commentors recommended additional substances for the Committee's consideration. About one-fifth of the commentors included comments on the methodology employed by the Committee in developing the PRELIMINARY LIST and about one-third included comments on other issues related to the Committee's activities. Such issues were the use of categories in the Committee's recommendations to EPA, documentation of the Committee's reasons for its decisions with respect to specific substances, and provision of opportunity for public comment on the Committee's actions.

Public comments on the PRELIMINARY LIST have been reviewed by the Committee and considered in the development of the Committee's initial recommendations. Four of the seven additional substances recommended by commentors were added to the PRELIMINARY LIST for consideration in selecting substances and categories for detailed review. Because of the large number of comments recommending deletions of substances from the Committee's consideration and the limited time available under the statutory deadline, pertinent comments were considered on a substance-by-substance or category-by-category basis during the Committee's review of preliminary dossiers and consideration of reasons for and against recommending testing. Comments on the Committee's methodology have been reviewed and will be considered in subsequent activities of the Committee. In the Committee's judgment, the recommended changes in methodology would not, if implemented, alter its initial recommendations. Comments dealing with use of categories, documentation of the Committee's reasons for actions, and other more general issues were also reviewed and considered in the development of the Committee's recommendations.

2.6 SELECTION OF SUBSTANCES FOR DETAILED REVIEW

This step of the Committee's procedure extended the scoring of the substances under consideration to factors (v) through (vii) of Section 4(e)(1)(A). These factors are:

> (v) the extent to which the substance or mixture is closely related to a chemical substance or mixture which is known to present an unreasonable risk of injury to health or the environment;
>
> (vi) the existence of data concerning the effects of the substance or mixture on health or the environment; and
>
> (vii) the extent to which testing of the substance or mixture may result in the development of data upon which the effects of the substance or mixture on health or the environment can reasonably be determined or predicted.

To accomplish this, each substance on the PRELIMINARY LIST was scored for each of seven biological activity factors by a number of experts available through the Committee's contract. The factors were: carcinogenicity, mutagenicity, teratogenicity, acute toxicity, other toxic effects such as reproductive effects or organ-specific toxicity, bioaccumulation, and ecological effects. After reviewing a summary of information on the biological activity of the substance developed by the contractor based on the open literature, each of the contractor's scorers assigned a score to the substance for the effect(s) for which that scorer was responsible.

A total of nine scorers was used by the contractor, with two or three scorers separately evaluating each effect in most cases. Each scorer considered both the summary information provided by the contractor and his personal knowledge of the substance and chemically-related substances in assigning scores. Any substantial discrepancies among individual scorers were identified, discussed among the scorers, and a consensus reached; in the case of minor discrepancies in the scores for any factor, the scores of the several scorers were averaged.

In addition, three of the effects (carcinogenicity, mutagenicity, and ecological effects) were separately scored by government experts from the National Cancer Institute, National Center for Toxicological Research, and Department of Interior, respectively. These scores were averaged with those of the contractor's scorers.

Scores assigned for the various effects took the form of either a numerical score (generally 0, 1, 2, or 3) or a letter score (generally x, xx, or xxx). Assignment of a numerical score indicated a judgment that further testing of the substance is not needed for the effect under consideration, while the magnitude of the score indicated the degree to which the effect had been confirmed or the dose level at which it had been found. Assignment of a letter score, on the other hand, indicated a judgment that further testing should be carried out, with the number of "x's" assigned reflecting a judgment as to the level of numerical score that might be anticipated after testing. For example, in scoring a substance for carcinogenicity a score of 3 meant that the substance is well established as a carcinogen in humans or experimental animals, while a score of xxx meant that the substance is strongly suspected of carcinogenic activity but has not been adequately tested. In averaging the scores assigned to a substance by the several scorers for a given factor, no mixing of numerical and letter scores was permitted. Any discrepancies between scorers in chosing the numerical or letter scale were discussed among the scorers and resolved. The criteria applied by the scorers in assigning scores for the various factors are described in more detail in Appendix D.

Categories of substances appearing on the PRELIMINARY LIST were not generally scored as entities, but rather, scores were assigned separately for each of the example substances listed under the category heading in the list.

Using these scores, the contractor provided the Committee a series of lists of the substances appearing on the PRELIMINARY LIST ranked according to various criteria. These included separate lists for each factor ranked by the average score a substance received for that factor (identifying those substances judged most in need for testing for a single effect) and a list ranked by the sum of the letter scores received by a substance for all factors (identifying substances requiring testing for a number of effects). Also tabulated on each list was an exposure index for each substance which was derived from the earlier scoring of production volume, environmental release, and occupational and general population exposure. For the human health effects factors and total letter score lists the exposure index used was the sum of the production volume, occupational exposure, and general population exposure scores, while for the bioaccumulation and ecological effects factors, the exposure index was the sum of the production volume and environmental release scores. The Committee also received from its contractor a list of those substances evaluated by the scorers which were known or might be anticipated to have additional adverse health or environmental effects as a result of contaminants appearing in the commercial product or degradation products of the substance under consideration.

The Committee's selection of substances and categories from the PRELIMINARY LIST to be carried forward for detailed review used the various lists provided by its contractor as guides, but reflected the independent judgments of the members of the Committee. First, the scores themselves were reviewed, with any major discrepancies between the contractor's scores and those of the government scorers or the judgments of individual Committee members being considered. Then, the Committee turned to the various ranked lists, reviewing in turn the substances ranked most in need of testing on the sum-of-letter-scores list or the lists for the individual factors. Each substance appearing in the top 75 to 100 positions on one or more of these lists was considered by the Committee and a decision made whether to select it for detailed review.

Particular attention was paid by the Committee to substances known or suspected to be carcinogens, mutagens, or teratogens, in keeping with the statutory guidance provided the Committee in Section 4(e)(1)(A) of TSCA. This emphasis was reflected not only in the Committee's consideration of individual substances and categories, but also in its structuring of the review process, since these effects were scored individually and, in effect, received greater attention than did other effects scored in groups (e.g., other toxic effects or ecological effects).

Categories of substances appearing on the PRELIMINARY LIST were also reviewed in terms of the scoring of their example members and the Committee's judgment as to retaining them. A number of decisions to modify previous categories or define new categories were made by the Committee during this review process.

In reviewing these lists, more than two-thirds of the individual substances scored by the contractor were explicitly considered by the Committee. Approximately eighty substances and categories were selected by the Committee for the drafting of preliminary dossiers and further detailed review. Of these, about half were individual substances and half categories.

2.7 CONSIDERATION FOR LISTING AND DESIGNATION

For each of the approximately eighty substances and categories selected for detailed review, preliminary dossiers have been (or are being) prepared by the Committee's contractor. Within the time period allowed by the statute for development of the Committee's initial recommendations, preliminary dossiers were drafted for about one-half of the substances and categories for detailed review. Consideration of these and other information resulted in the initial recommendations transmitted by this report. Consideration of the remaining substances and categories already selected for detailed review, and others which may subsequently be selected, will continue and will be reflected in subsequent recommendations to EPA by the Committee.

The preliminary dossiers summarized information obtained from the open literature relating to the identification, relevant chemical and physical properties, production volume, uses, environmental release, and exposure to the substance under consideration as well as information on the nature and findings of previous studies of its human health and environmental effects. Information on the biological activity of other chemically similar substances was also included where available. Preliminary dossiers for categories of substances included these types of information for specific members of the category, generally the example members identified in the PRELIMINARY LIST.

Using the information summarized in the preliminary dossier, together with information submitted in public comments on the PRELIMINARY LIST, information available to the Committee from various Federal agencies, and the members' individual knowledge, the Committee reviewed each substance or category. Each of the factors specified in Section 4(e)(1)(A), as well as any other relevant factors identified by the Committee on a case-by-case basis, was considered. In particular, in considering factor (vi) of Section 4(e)(1)(A), the existence of data concerning the effects of the substance on helath or the environment, the Committee considered test programs currently in progress, as well as data already generated. Another factor considered in certain instances was the status of current regulatory action relative to the substance. In each case where a category of substances was under consideration the appropriate definition of the category and the need for data on all members of the category were considered. Where relevant to the particular type of testing under consideration for a substance or category, factor (viii) of Section 4(e)(1)(A), the availability of test facilities and personnel, was discussed on a case-by-case basis. In general, however, this factor was considered in the aggregate after the Committee's tentative recommendations for all substances and categories had been identified. The Committee's consideration of this factor is discussed further in section 2.8 of this report.

After reviewing and thoroughly discussing the information available to the Committee on the substance or category under consideration, a decision was made regarding whether to recommend the development of test rules by EPA and, if so, for which effects. Subsequently, one or more Committee members participated in the drafting of the supporting reasons for each recommendation and these reasons were again reviewed by the Committee. A final decision to recommend the substance or category for testing represents a consensus by the Committee members that such testing is needed to evaluate the effects of the substance (or of each individual substance falling within the definition of a category) on human health and the environment, and that priority attention should be given by EPA to requiring the conduct of such testing. The Committee recognized, of course, that some members of recommended categories may have already been adequately tested for the effects of concern and would not require further testing.

Several substances and categories reviewed by the Committee were deferred for further consideration because of insufficient information to adequately define the categories or to determine the needs for testing.

Assignment of priority order to the substances and categories recommended for testing was also considered. The Committee concluded that all of the substances and categories being recommended at this time should be given equal priority in EPA's development of test rules. Factors contributing to this decision were the limited number of recommendations being made, the Committee's decision to designate all recommended substances and categories for consideration by EPA within 12 months, and the Committee's understanding of EPA's plans to develop its test rules for various effects, e.g., carcinogenicity, rather than for individual substances or categories. The Committee recommends that these substances and categories be included in the first applicable "effects rule".

2.8 CONSIDERATION OF AVAILABILITY OF TESTING FACILITIES AND PERSONNEL

One of the criteria listed in Section 4(e)(1)(A), that the Committee was required to consider, is the reasonably foreseeable availability of facilities and personnel for performing the testing it recommends. The Committee reviewed the results of recent surveys of toxicology testing capabilities conducted by the Society of Toxicology (SOT) and the DHEW Committee to Coordinate Toxicology and Related Programs (CCTRP). While the SOT surveyed general toxicology testing capabilities, the CCTRP specifically assessed inhalation test capabilities. The Committee also reviewed the capabilities and plans of the National Center for Toxicological Research (NCTR), the possible impact of the FDA's Good Laboratory Practices, and the logistics and practical considerations for carcinogenicity, mutagenicity, and reproductive effects testing. It also was briefed on ecological test capabilities and needs in that area.

Based upon these reviews, the Committee has concluded that there are sufficient toxicology testing capabilities in the U.S. to carry out the health effects testing recommended by the Committee in this report.

A more difficult area to assess was that of environmental or ecological testing. Capabilities for acute studies are probably adequate, but the National capability for conducting long-term tests of chemical pollution on the environment will be less certain until the test standards and protocols are defined through the rulemaking process. The Committee feels, however, that the testing burden likely to result from recommendations in this report is reasonable.

CHAPTER 3. RECOMMENDATIONS OF THE COMMITTEE

3.1 SUBSTANCES AND CATEGORIES OF SUBSTANCES RECOMMENDED FOR TESTING

As described in Chapter 2 of this report, the Committee has, with the assistance of a technical support contractor, carried out a multi-step screening procedure to identify for its detailed review a limited number of substances and categories of substances likely to have priority for testing to determine their effects on human health and the environment. A number of substances and categories identified by this process have been reviewed by the Committee, which has given careful consideration to each of the eight factors specified in Section 4(e)(1)(A) of TSCA. The Committee has also considered such other factors as it judged relevant on a case-by-case basis. Such additional factors have included test programs currently in progress, the current status of regulatory action with respect to a substance, and the need for test data on all members of certain categories rather than on one or more individual members of the category.

The eighth factor specified in Section 4(e)(1)(A) for the Committee's consideration, the reasonably foreseeable availability of facilities and personnel for performing the recommended testing, has (as described in Section 2.8 of this report) been considered by the Committee with respect to the aggregate requirements of all of the testing recommendations made here, as well as for each individual testing recommendation. In the Committee's judgment there are, or can be made available within the next few years, adequate facilities and personnel for conducting the testing now being recommended by the Committee. Furthermore, any specific limitations of facilities or personnel which cannot now be identified by the Committee would be expected to be short-term in nature and can be taken into account by EPA in establishing the time periods for submission of the test data under Section 4(b)(1).

In selecting substances and categories for inclusion in its initial recommendations, the Committee has also given priority attention to substances known or suspected to cause cancer, gene mutations, or birth defects.

Based on its consideration of the factors identified in Section 4(e)(1)(A) and all other relevant factors identified by the Committee, and using all of the information available to it, including the knowledge and professional judgment of its members, it is the consensus of the TSCA Interagency Testing Committee that the ten substances and categories of substances listed in the accompanying table should be given priority consideration by the Administrator of the Environmental Protection Agency for the promulgation of regulations under Section 4(a) requiring the conduct of the types of testing specified. Each of these substances and categories is designated by the Committee for consideration by EPA within the next 12 months.

SUMMARY OF TESTING RECOMMENDATIONS
BY THE
TSCA INTERAGENCY TESTING COMMITTEE

Substance or Category	Types of Testing Recommended					
	Carcinogenicity	Mutagenicity	Teratogenicity	Other Chronic Effects	Environmental Effects	Epidemiological Study
Alkyl Epoxides	X	X	X	X	X	X
Alkyl Phthalates					X	
Chlorinated Benzenes, (Mono- and Di-)	X	X	X	X	X	X
Chlorinated Paraffins	X	X	X	X	X	
Chloromethane	X	X	X	X		
Cresols	X	X	X	X	X	
Hexachloro-1,3-butadiene					X	
Nitrobenzene	X	X			X	
Toluene	X		X	X		X
Xylenes		X	X			X

Table 1

In listing and designating these ten substances and categories, the Committee has decided that all should be given equal priority by EPA in the development of test rules under Section 4(a) of TSCA. All are of high priority and should be included in the first applicable "effects rule" (e.g., carcinogenicity) developed by EPA.

In selecting categories of substances for inclusion in its recommendations, the Committee recognizes that some members of a category may have already been adequately tested for one or more of the effects listed; in such cases no additional testing would be required. The Committee also recognizes that the precise definition of each category will have to be considered and decided by EPA in developing its test rules.

The Committee's reasons for including each substance or category of substances on its list of recommendations, which are required by Section 4(e)(1)(B) to be submitted with the Committee's recommendations, are presented in the following section. In addition, the Committee will forward to EPA in the next few weeks a dossier on each substance or category included on the Committee's list of recommendations. These dossiers will summarize the information pertaining to each substance or category which was considered by the Committee in making its decision to recommend testing.

3.2 REASONS FOR RECOMMENDING TESTING OF THE SUBSTANCES AND CATEGORIES

The ten substances and categories which the Committee has designated for consideration by the EPA Administrator for development of test rules within twelve months are listed below with the Committee's reasons for recommending them.

3.2.A ALKYL EPOXIDES

TESTING RECOMMENDATIONS:

Carcinogenicity
Mutagenicity
Teratogenicity
Other Chronic Effects
Environmental Effects
Epidemiology

CATEGORY IDENTIFICATION: This category includes all noncyclic aliphatic hydrocarbons with one or more epoxy functional groups.

REASONS FOR RECOMMENDATIONS:

Production, Release and Exposure: Although these compounds are generally used as industrial intermediates, several alkyl epoxides are produced in very large quantities (e.g., ethylene oxide at over 4 billion pounds per year). The vast amounts produced thus raise concerns primarily with respect to workplace exposure. The reactivity of these compounds is such that environmental persistence is not anticipated; however, their reaction products may be of significance.

EFFECTS OF CONCERN: The epoxy structure is a relatively reactive functional group which is believed to be the source of the carcinogenic and mutagenic activity which is well characterized for several members reviewed (particularly the diepoxides). Thus, while some members of the group appear to be relatively well characterized as potential mutagens and/or carcinogens, these results and the presence of the epoxy functional group raise the need for testing other compounds in this group for these and other effects.

Carcinogenicity: Diepoxides are demonstrated carcinogens in animal studies. Ethylene oxide proved inactive while propylene oxide showed carcinogenic activity in mice. Other alkyl epoxides are less well tested. Because of the alkylating properties of these compounds it is recommended that alkyl epoxides be tested for carcinogenic potential. Mutagenicity of most members of this group tested provides further concern for carcinogenic potential.

Mutagenicity: Because most members of this group which have been tested proved to be mutagenic; other members of this group should be tested for this effect.

Teratogenicity: In general, these compounds have not been adequately tested for teratogenicity but should be, considering the reactivity of the epoxy group toward biological materials.

Other Chronic Effects: Because of the reactivity of epoxides with biological materials, they should be tested for specific chronic organ effects and behavioral changes.

Environment Effects: While the persistence of these compounds as epoxides is not great, concern is expressed for reaction products. In view of this possibility, the fate of epoxides in the environment should be determined through testing.

Epidemiology: Because of the large scale production of several of these compounds, and because of the strong toxicological evidence of possible carcinogenic and mutagenic effects, the Committee recommends that retrospective epidemiologic studies be required for two or three of the highest exposure compounds when suitable cohorts can be identified.

3.2.B ALKYL PHTHALATES

TESTING RECOMMENDATIONS:

Environmental Effects

CATEGORY IDENTIFICATION: This category consists of all high production (e.g., 10 million lbs/yr or greater) alkyl esters of 1,2-benzene dicarboxylic acid (orthophthalic acid).

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: Many of these compounds are produced in large volume, some of them over one hundred million pounds per year. Their use as plasticizers in a wide variety of products results in large volumes of alkyl phthalates reaching the aquatic environment either as wastes from formulating plants or from use and disposal of end products.

Effects of Concern:

Environmental Effects: Many of the alkyl phthalates are quite stable, breaking down only slowly to monophthalates or phthalic acid. There has been a great deal of information published on their environmental fate and toxicity to aquatic organisms. Some are known to have considerable toxicity to fresh water fish. In view of the large volume in which they can be expected to reach the aquatic environment and persist and accumulate in aquatic organisms, it is important to have data on the toxicity to aquatic organisms of all high production alkyl phthalates. Each such compound should be tested for chronic toxicity to typical aquatic organisms, especially fish. Effects on reproduction (or population) should be included in this testing.

3.2.C CHLORINATED BENZENES, MONO- AND DI-

TESTING RECOMMENDATIONS:

Carcinogenicity
Mutagenicity
Teratogenicity
Other Chronic Effects
Environmental Effects
Epidemiology

CATEGORY IDENTIFICATION: This category consists of four closely-related chemical substances: monochlorobenzene (CAS No. 108-90-7), and ortho-, meta-, and paradichlorobenzene (CAS Nos. 95-50-1, 541-73-1, and 106-46-7).

REASONS FOR RECOMMENDATIONS:

Production, Release and Exposure: The chlorobenzenes are produced in large quantities, monochlorobenzene over 300 million pounds/year and ortho- and para-dichlorobenzene approximately 50 million pounds each. These chemicals are widely used in industrial processes, as solvents, and in many consumer products. Therefore, the exposure and potential for hazard is great, particularly in light of their high release rate and anticipated persistence in the environment.

Effects of Concern:

Carcinogenicity: One very limited animal study suggested the induction of sarcomas following subcutaneous injections of para-dichlorobenzene. A possible association of several cases of leukemia with human exposure to mixtures of ortho- and para-dichlorobenzenes has also been reported. These studies, as well as other animal toxicity experiments, do not provide sufficient data on which to assess the carcinogenic potential of members of this class.

Mutagenicity: While a study has demonstrated back mutations in yeast exposed to ortho-dichlorobenzene, the data are inadequate to assess the potential mutagenic hazard. Additional testing is needed in view of the widespread release and exposure. The other chemicals in this class should also be tested for mutagenicity.

Teratogenicity: While teratogenic effects are suspected for certain higher chlorobenzenes, the mono- and dichlorobenzenes have not been adquately tested.

Other Chronic Effects: Liver, kidney, respiratory and neurological effects have been observed with high level exposures. Effects at lower levels cannot be characterized from existing data. Chronic studies should be undertaken.

Environmental Effects: The environmental fate of these compounds should be determined. Evidence exists for environmental pollution and bioaccumulation in aquatic life. The effects are unknown. Studies should be initiated to assess the impact of these chemicals on terrestrial and aquatic systems.

Epidemiology: A possible link has been made between exposure to ortho- and para-dichlorobenzene and leukemia. Further efforts to evaluate chronic effects should be made by the identification and evaluation of specific populations who are or have been exposed to either ortho- or paradichlorobenzene.

3.2.D CHLORINATED PARAFFINS, 35-64% CHLORINE

TESTING RECOMMENDATIONS:

Carcinogenicity
Mutagenicity
Teratogenicity
Other Chronic Effects
Environmental Effects

CATEGORY IDENTIFICATION: This category is comprised of a series of mixtures of chlorination products of materials known commercially as paraffin oils or paraffin waxes; those having a chlorine content of 35% through 64% by weight are included.

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: The 1972 annual production of chlorinated paraffins was about 80 million pounds. The use of these materials in a wide variety of household and paint products, as well as adhesives and flame retardants, results in an estimated release rate of about 50 million pounds per year.

Effects of Concern:

Human Health Effects: A chronic study in mice showed evidence of degenerative changes in the liver and spleen; no data are available on the carcinogenicity, mutagenicity, teratogenicity, or other chronic effects of these mixtures. The Committee recommends that commercial products in this category be tested for such effects.

Environmental Effects: The occurrence of residues of chlorinated paraffins in fish indicates the need for critical assessment of the biological significance of this contamination of the aquatic environment. The persistence, environmental fate, and chronic effects on aquatic organisms of the chlorinated paraffins should be determined by appropriate testing.

3.2.E CHLOROMETHANE

TESTING RECOMMENDATIONS:

Carcinogenicity
Mutagenicity
Teratogenicity
Other Chronic Effects

SUBSTANCE IDENTIFICATION: CAS No. 74-87-3

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: The 1974 U.S. production of chloromethane was over 350 million pounds, most of this being used as a synthetic intermediate. However, it is estimated that about 5% of the annual production (over 15 million pounds per year) is released into the environment. NIOSH estimates that the number of workers exposed to chloromethane numbers about 31,000.

Effects of Concern:

Carcinogenicity: To date, chloromethane has not been the subject of a carcinogenicity study, although it is structurally related to chloroform, carbon tetrachloride, and iodomethane, all of which have been reported as being carcinogenic. Moreover, chloromethane has recently been reported as exhibiting mutagenic properties in the Salmonella mutagenic test with microsomal activation.

Mutagenicity: The initial positive results in the Salmonella mutagenic test with microsomal activation should be supplemented with test data regarding chromosomal abberrations.

Teratogenicity: The absence of data in this area, coupled with known toxic effects, calls for the initiation of studies to determine the extent of the potential hazard to the reproductive system and the fetus.

Other Chronic Effects: Exposure to chloromethane has been implicated in damage to the central nervous sytem, liver, kidneys, bone marrow and cardiovascular systems. Effects on these systems should be examined in chronic toxicity tests.

3.2.F CRESOLS

TESTING RECOMMENDATIONS:

- Carcinogenicity
- Mutagenicity
- Teratogenicity
- Other Chronic Effects
- Environmental Effects

CATEGORY IDENTIFICATION: This category consists of the three isomers of methyl phenol: ortho-cresol (CAS No. 95-48-7), meta-cresol (CAS No. 108-39-4), and para-cresol (CAS No. 106-44-5).

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: Cresols are produced in large quantities, having a combined U.S. production in 1975 of about 90 million pounds. An annual release rate of about 45 million pounds has been estimated. Their wide use as industrial solvents leads to substantial occupational exposure. NIOSH estimates that roughly two million workers are exposed to cresols. In addition, cresols are used in many consumer products, resulting in a large general exposure.

Effects of Concern:

Carcinogenicity: Cresols have not been evaluated for carcinogenicity. Because of widespread exposure and suggestive evidence of mutagenic effects in certain plants, cresols should be tested for carcinogenicity.

Mutagenicity: There is some suggestion of the mutagenic potential of cresols in certain plants, but its potential as a human mutagen has not been assessed. It is, therefore, recommended that further mutagenic studies be conducted.

Teratogenicity: The teratogenicity of the cresols has not been assessed, but such testing is needed in view of the evidence of biological activity of cresols (see Other Chronic Effects, below) and their widespread exposure.

Other Chronic Effects: Although toxic effects involving the central nervous system, lungs, kidneys, liver, pancreas, and spleen have been observed following acute exposure to cresol-containing products, adequate testing of cresols for chronic effects following prolonged exposure has not been reported and should be conducted.

Environmental Effects: There is evidence that creosote oils containing cresols are acutely toxic to fish and taint fish flesh at low concentrations. Because of their substantial release into the aquatic environment, cresols should be tested for chronic effects on fish and other aquatic organisms.

3.2.G HEXACHLORO-1,3-BUTADIENE

TESTING RECOMMENDATIONS:

Environmental Effects

SUBSTANCE IDENTIFICATION: CAS No. 87-68-3

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: Although the most recent (1974) data available indicate that this compound is no longer commercially manufactured in the U.S., it continues to be produced as a waste byproduct of various chlorination processes and is also imported into the U.S. for industrial solvent use. The release of hexachlorobutadiene into the environment has not been quantified, but there is good evidence of widespread distribution in the aquatic environment.

Effects of Concern:

Environmental Effects: Hexachlorobutadiene's human health effects are being studied in depth. It is a stable substance which is widely distributed in the aquatic environment and has been reported to bioaccumulate in fish and other aquatic organisms. These factors indicate that hexachlorobutadiene should be tested to determine its fate in aquatic systems and its effects on invertebrates, fish, higher vertebrates, and plant life in aquatic systems. Its appearance in some European agricultural products suggests that its uptake by plants and/or foraging species should also be studied.

3.2.H NITROBENZENE

TESTING RECOMMENDATIONS:

Carcinogenicity
Mutagenicity
Environmental Effects

SUBSTANCE IDENTIFICATION: CAS No. 98-95-3

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: U.S. production of nitrobenzene in 1975 was about 400 million pounds. Its release to the environment has been estimated to be about 20 million pounds annually. Although its predominant use (97 percent of production) is in closed systems in aniline manufacture, nitrobenzene is also an industrial solvent and dye intermediate. General population exposure can arise from environmental release, and from dispersive uses such as perfume in soap; cleaner for woodwork, wood flooring and paneling; ingredient of metal polishes and shoe blacking. Nitrobenzene liquid and vapor penetrate intact skin readily, and the efficiency of vapor absorption by inhalation is high.

Effects of Concern:

Carcinogenicity: No information is available on the carcinogenicity of nitrobenzene. Since it is biologically active, producing cellular changes,
nitrobenzene should be tested for
carcinogenicity.

Mutagenicity: Although there is evidence of its biological activity, no mutagenicity testing has been reported for nitrobenzene. Mutagenicity testing should be performed.

Environmental Effects: Nitrobenzene is a relatively persistent substance in the environment. Its low volatility, stability to light, and low water solubility indicate that bioaccumulation is possible. Acute effects have been demonstrated in fish. Nitrobenzene inhibits oxygen utilization and hydrogen sulfide production in sewage microorganisms, inhibits growth in yeast, and is toxic to various soil bacteria and microorganisms. Additional data are needed to adequately characterize the persistence and fate of nitrobenzene and its matabolites in the aquatic environment. Testing is needed for such characteristics as well as to determine the effects of chronic exposure to nitrobenzene on fish, aquatic invertebrates, aquatic plant life, and waterfowl.

3.2.I TOLUENE

TESTING RECOMMENDATIONS

Carcinogenicity
Teratogenicity
Other Chronic Effects
Epidemiology

SUBSTANCE IDENTIFICATION: CAS No. 108-88-3

REASONS FOR RECOMMENDATIONS:

Production, Release and Exposure: Toluene is produced in large quantities with an annual production rate in excess of 5 billion pounds. Because of its widespread use as a solvent, as well as a multiplicity of other uses, toluene has an unusually high occupational exposure (over 1 million workers). Its presence in many consumer products leads to a large general exposure. Toluene is currently being substituted for many benzene-uses and has an annual release rate exceeding 1 billion pounds.

Effects of Concern:

Carcinogenicity: Previous studies based solely on skin application techniques in animals have demonstrated a carcinogenic potential for toluene. Some of these studies were limited in design and prevented an appropriate appraisal of the carcinogenic hazard of toluene. It is, therefore, recommended that testing be conducted in long-term animal experiments taking into consideration the appropriate route of exposure.

Teratogenicity: Information is lacking on the teratogenic hazard of this chemical, thus necessitating the initiation of studies to determine if toluene is teratogenic.

Other Chronic Effects: Liver, central nervous system and hematopoietic effects have been observed at high level exposures. Effects at lower levels cannot be characterized from existing data. Chronic studies to evaluate the effects of prolonged exposures are recommended.

Epidemiology: Occupational studies have been conducted predominantly on the acute toxic effects of toluene. There is little information on chronic effects in humans from exposure to low levels of toluene over an extended period of time. Because of its long-term use, high human exposure, and demonstrated effects in animals, epidemiological studies may be particularly important in assessing the human health effects of toluene.

3.2.J XYLENES

TESTING RECOMMENDATIONS:

Mutagenicity
Teratogenicity
Epidemiology

CATEGORY IDENTIFICATION: This category consists of the three isomers of dimethyl benzene: ortho-xylene (CAS No. 95-47-6), meta-xylene (CAS No. 108-38-3), and para-xylene (CAS No. 106-42-3)

REASONS FOR RECOMMENDATIONS:

Production, Release, and Exposure: In the aggregate, approximately 8 billion pounds of xylenes are produced each year. Approximately 900 million pounds are released to the environment each year. Mixed xylenes were ranked by NIOSH 13th out of approximately 7000 agents in terms of the number of workers exposed. Xylenes are also used in a wide variety of consumer products, resulting in general population exposures.

Effects of Concern:

Mutagenicity: Mutagenesis tests have not been reported for any of the xylenes, but should be conducted in view of widespread exposure and evidence of toxic effects to several organ systems.

Teratogenicity: Xylenes cross the placental barrier and, according to two Russian studies, are embryotoxic. Therefore, they should be tested for teratogenicity.

Epidemiology: Because of their long-term use, high human exposure, and demonstrated effects in animals, epidemiological studies may be particularly important in assessing the human health effects of xylenes and should be conducted.

APPENDIX A

DATA SOURCES USED FOR PREPARATION OF THE INITIAL LIST

01 Toxic Pollutants in Point Source Water Effluent Discharge

This list of 120 chemicals and categories consists of Appendices A and C of the settlement agreement dated 7 June 1976 between the Environmental Defense Fund and EPA. It is a priority list of toxic pollutants subject to regulations through point source effluent limitations (Section 307(a)) under the Federal Water Pollution Control Act.

02 Scoring of Organic Air Compounds, June 1976, MITRE, MTR-6248

This list of 337 chemicals and categories was compiled and documented by MITRE (September 1976) under contract to EPA. The relevant factors in selecting chemicals for the list were: (1) quantity produced, (2) potential for atmospheric release, and (3) toxicological effects.

03 Final Report of NSF Workshop Panel to Select Organic Compounds Hazardous to the Environment, April 1975

This list of 80 chemicals and categories was compiled and documented by Stanford Research Institute under contract to the National Science Foundation. The list consists of those chemicals having the greatest potential for environmental release, selected from the universe of manufactured organic chemicals with the highest calculated release rates.

04 Potential Industrial Carcinogens and Mutagens

This list of 88 chemicals has been compiled by the National Center for Toxicological Research. The list is made up of industrial compounds which are potential carcinogens and/or mutagens, and which have been selected based upon available data concerning activity, use, production, and population at risk.

05 Occupational Carcinogens for Potential Regulatory Action

This list of 116 chemicals and categories was compiled by OSHA from suspected carcinogens. Selection was based primarily upon data available through the NIOSH Registry (Source List 13).

07 Chemicals Tested or Scheduled for Testing at the Fish-Pesticide Research Laboratory, Department of Interior

This list consists of 174 toxic chemicals which are suspected of being hazardous to fish and wildlife.

08 Substances with Chronic Effects other than Mutagenicity, Carcinogenicity, or Teratogenicity; A Subfile of the NIOSH Registry

A subfile of the NIOSH Registry (Source List 13)

09 Criteria Documents Prepared or Planned by NIOSH, February 24, 1977

This list of 127 chemicals and categories consists of substances for which criteria documents have been or will be prepared and delivered to the Department of Labor. In selecting these chemicals NIOSH considered: a) the number of workers exposed, b) known or suspected toxic effects, and c) physical and chemical properties.

10 Suspected Carcinogens; A Subfile of the NIOSH Registry

This is a list of 1,900 chemicals and categories which have been reported to have produced cancer in test animals. The list is included in Source List 13.

11 Suspected Mutagens; A subfile of the NIOSH Registry

This is a list of approximately 100 chemicals and categories which have been reported to have produced mutagenic effects in test systems. This list is included in Source List 13.

*

13 NIOSH Registry of Toxic Effects of Chemical Substances, 1976

This list of 21,543 chemicals and categories was compiled and documented in the NIOSH Registry. Only those substances which were on Source Lists 8, 10, 11, or 12 were included in the INITIAL LISTING.

17 The Ecological Impact of Synthetic Organic Compounds on Estuarine Ecosystems, September, 1976, EPA-1600/3-76-075

This list of 9 chemicals was compiled as part of a study of the impact of synthetic organic compounds on estuarine ecosystems. The effects of the 9 chemicals and a number of pesticides were analyzed and documented in the study.

18 Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1976, American Conference of Government Industrial Hygienists

This list of approximately 570 chemicals and categories was compiled by the ACGIH to give Threshold Limit Values for chemical substances and physical agents in the workroom environment.

19 National Occupational Hazard Survey (1972-1974)

This list of over 7,000 chemicals and other hazards has been compiled by NIOSH. These hazards are ranked according to the estimated number of workers exposed. Only the chemicals ranked among the top 500 hazards were included in the INITIAL LISTING.

20 Chemicals Being Tested for Carcinogenicity by the Bioassay Program, DCCP, National Cancer Institute, 1977

This list of 372 chemicals includes those which have been selected for bioassay by the National Cancer Institute.

* 12 See Page 31a

21 EPA/Office of Toxic Substances List of Priority Toxic Chemicals, 1977

This list of 162 chemicals was compiled by EPA/OTS from the NIOSH list of carcinogens (Source List 10).

22 A Study of Industrial Data on Candidate Chemicals for Testing, EPA Contract # 68-01-4109, November, 1976

This list of 650 chemicals and categories was compiled by Stanford Research Institute as part of the contracted effort to produce Source List 03. Production and calculated release data are included.

24 General List of Problem Substances, Environmental Contaminants Committee, Ottawa, Ontario, Canada, 1977

This list of 160 chemicals and categories of environmental concern was compiled by the Canadian government.

OTHER LISTS USED FOR REFERENCE BUT NOT USED AS SOURCE LISTS FOR THE INITIAL LISTING:

06 Survey of Compounds which have been Tested for Carcinogenic Activity (Index, 1970-1971), NIH/HEW

This list of 3,634 chemicals and categories is a cumulative index by CAS number of PHS 149 volumes through 1970-1971.

14 Research Project to Gather and Analyze Data and Information on Chemicals that Impact Man and the Environment

This list of 3,200 chemicals and categories was compiled and documented by Stanford Research Institute under contract to the National Cancer Institute. The documentation includes total production and calculated release data for each of the chemicals in nine hazard categories: (1) over-the-counter drugs, (2) prescription drugs, (3) cosmetics, (4) trade-sales paints, (5) water pollutants, (6) air pollutants, (7) soaps and detergents, (8) pesticide residues in food, and (9) intentional food additives.

16 Other Potential Modifiers of the Stratosphere, 1975

This list of 41 chemicals was compiled by the National Institute of Environmental Health Sciences from the universe of 275 manufactured chemicals ranked for release rate used by Stanford Research Institute in preparing Source List 03. This list identifies potential modifiers of the stratosphere and provides related information.

23 EPA/Office of Research and Development, Chemical Production

A set of production data compiled by EPA/ORD on approximately 140 chemicals.

12 Suspected Teratogens; A subfile of the NIOSH Registry

This is a list of approximately 200 chemicals and categories which have been reported to have produced teratogenic effects in test animals. This list is included in Source List 13.

APPENDIX B

PRODUCTION, RELEASE, AND EXPOSURE SCORES

A. The production, environmental release, occupational exposure, and general population exposure factors described in the text were scored in the following manner: in the following manner:

Factor 1: Production

Annual production data were collected from a number of sources:

a. Scoring of Organic Air Compounds (Source List 02 of Appendix A)

b. A Study of Industrial Data on Candidate Chemicals for Testing (Source List 22 of Appendix A)

c. EPA/OR&D Chemical Production (Source List 23 of Appendix A)

d. Synthetic Organic Chemicals, United States Production and Sale, 1975, United States International Trade Commission

e. Chemical Economics Handbook, 1975 Stanford Research Institute

f. Chemical and Engineering News: Vol. 52, No. 51, dated 12/23/74; Vol. 55, No. 18, dated 5/2/77; Vol. 55, No. 24, dated 6/13/77

The Factor 1 score assigned to a chemical was the common logarithm of the highest annual production value (in millions lbs/yr) found in any of the above sources. If an annual production value was not available for a chemical in any of these sources, a Factor 1 score of -0.5229 (corresponding to an assumed annual production of 300,000 pounds) was assigned.

Factor 2: Quantity Released into the Environment

The quantity of chemical released into the environment was scored on a scale from 0 to 3 as follows:

Score	Release Rate	Estimate Based on Uses
3	>30 percent	Mostly dispersive uses
2	3 to 30 percent	Some dispersive uses
1	.3 to 3 percent	Few dispersive uses; or primarily industrial chemical with propensity for leaks
0	<.3 percent	Well contained industrial chemical

Estimates of release rates for a number of chemicals are given in Source List 22 of Appendix A. For those chemicals for which no release rates were given, an estimate was made on the basis of the dispersive nature of the chemical's uses as indicated in the above table.

An estimate was also made of the chemical's persistence according to the following table:

Score	Lifetime	Example
3	Infinite (years or greater)	Compounds of metals, freons, CCl_4, N_2O, SF_6, many polymers
2	Order of 1 year	Tetrachloroethylene, flame retardants, phthalate esters, silicones
1	Order of a few days	SO_2
0	Hours or less	Reactive compounds

The sum of the scores of the two subfactors, release quantity and persistence, was taken as an indication of the environmental burden posed by the chemical.

Factor 3: Occupational Exposure

The source of data on occupational exposure to chemicals was the National Occupational Hazard Survey (NOHS) conducted by the National Institute for

Occupational Safety and Health. In this survey, the approximately 7000 most common hazards occurring in the working place were rank ordered. To achieve an occupational exposure score with a range and direction similar to those of the other factors, the Factor 3 score assigned to a chemical was 3.8451 minus the common logarithm of its rank on the NOHS list. (3.8451 is the logarithm of 7000.) Chemicals which did not appear on the NOHS list were given a score of zero, equivalent to having been ranked number 7000 on the survey.

Factor 4: Extent to Which the General Population is Exposed

Four individual subfactors were scored and then summed to measure the general population exposure. The four subfactors were scored as follows:

SUBFACTOR 1 Number of people exposed to the chemical (exclusive of a workplace environment)

Score	No. of People	Example
3	$>20 \times 10^6$	Widely used household products (e.g., wearing apparel, shoe polish, certain surface coatings, common paints and their solvents, common plastics and their additives, detergents, furnishings and carpets, wood cleaning products, refrigerants, natural gas, nonfood packaging materials, flame proofers) General air, food and water contaminants Automotive products (e.g., gasoline and additives, rubber, surface coatings, plasticizers, flame proofers) Products used widely in commercial buildings (mostly same as household, including commercial cleaners, disinfectants)

Score	No. of People	Example
2	$2\text{-}20 \times 10^6$	Less widely used household products (e.g., uncommon paints, specialty apparel such as baby wear, hobby uses, arts and crafts, tools) Regional air and water pollutants, farm chemicals (exclusive of pesticides)
1	$0.2\text{-}2 \times 10^6$	Specialty hobbies (e.g., photography), specialty products Neighborhood air and water pollutants from local industries
0	$< 2 \times 10^5$	Chemical intermediates rarely found outside the workplace

SUBFACTOR 2 Frequency of exposure (to the typical person in ranking number of people exposed under Subfactor 1)

Score	Frequency	Exampless
3	Daily or more often	General air, food and water contaminants, household products in regular use, material used inside automobiles, clothing
2	Weekly	Hobby crafts, household products used intermittently (e.g., certain cleaners), bleaches, gardening products
1	Monthly	Dry cleaning, certain solvents, house maintenance (e.g., polishes, certain cleaning agents), automobile maintenance
0	Yearly or less frequently	Application of household paints, specialty products

SUBFACTOR 3 Exposure intensity. This is intended to reflect the tot 1 amount of material that comes into contact with the average or typical person whose exposure has been scored under subfactors 1 and 2. Scoring of this factor considered the number of grams of the material that makes contact with the average person in the course of one exposure (daily, weekly, monthly or yearly as scored in subfactor 2). Thus, for example, a trace pollutant may lead to exposure of a typical person of the order of micrograms per day every day; use of a specialty solvent might lead to exposure of a typical person of the order of grams per day once a year: these would be scored 3,0 and 0,3 respectively on subfactors 2 and 3.

Score	Intensity	Examples
3	High (10^{-1} or more grams per exposure)	Plastics, fabrics, surface coatings, volatile solvents in closed spaces, liquids contacting skin, high concentration gases
2	Medium (10^{-1} to 10^{-2} g per exposure)	Fabric additives, solvents in open spaces or outdoors, dusts, solutes, transitory exposures to vapors or aerosols
1	Low (10^{-3} to 10^{-4} g per exposure)	Low level indoor exposure, volatile substances from home furnishings and building materials (e.g., plasticizers, flame proofers), low volatility solvents, pigments
0	Very low (less than 10^{-5} g per exposure	Environmental contaminants (low level air, food, and water contaminants), monomers in polymers

SUBFACTOR 4 Penetrability. This is a measure of the material that comes into contact with a person (whether by dermal, inhalation, or ingestion exposure) and that is expected to be absorbed into the body (even transitorily) with potential for interaction with cells.

Score	Penetrability	Examples
3	High (10 to 100% absorption)	Organic solvents in liquid, mist, or aerosol form, vapors and gases if likely to be soluble in body fluids, respirable-sized particles, surface active agents, materials known to have high dermal systemic toxicity
2	Medium (1 to 10% absorption)	Solvents with low volatility and/or larger molecules, organic materials in water solution, waxes and polishes, coarse dusts
1	Low (0.01 to 1% absorption)	Certain solids, dermal exposure to most inorganic materials in water solution
0	Neglegible (less than 0.01% absorption)	Polymers, metals

B. In making the judgments called for in scoring Factors 2 and 4 above, knowledge of the chemical's uses was necessary. Use information was collected from the following sources:

1. The Condensed Chemical Dictionary, Ninth Edition, Hawley, Van Nostrand Reinhold Company, New York, 1977.
2. The Merck Index, Ninth Edition, Merck and Company, Inc., Rahway, N.J., 1976.
3. Faith, Keyes, and Clark's Industrial Chemicals, Lowenheim and Moran, Fourth Edition, J. Wiley and Sons, Inc., New York, 1975.
4. Chemical Marketing Reporter, Schnell Publishing Company, Inc., New York.
5. Encyclopedia of Chemical Technology, Kirk-Othmer, Inter-Science Publishing Company, New York, 1972.

APPENDIX C

ORDERING THE CHEMICALS BASED ON PRODUCTION, RELEASE, AND EXPOSURE

A linear weighting scheme was used to rank order the chemicals. The rank of the j^{th} chemical, r_j, was computed by the formula:

$$r_j = \sum_{i=1}^{4} w_i \frac{f_{ij}}{s_i} ,$$

where w_i is the weight assigned to the i^{th} factor,

f_{ij} is the i^{th} factor score of the j^{th} chemical,

and s_i is a scaling factor chosen to normalize the assigned scores.

The four scaling factors employed were:

s_1 = log 20,850 - 4.3191; 20,850 million lb/yr being the maximum of all Factor 1 chemical production quantities.

s_2 = 6; 6 being the maximum of all Factor 2 environmental release scores.

s_3 = 3.8451 - log 3 = 3.3680; third being the highest NOHS rank among the scored chemicals. (Ranked first and second on the NOHS list were continuous noise and mineral oil, the former not being a chemical hazard and the latter not being among the scored chemicals.)

s_4 = 12; 12 being the maximum of all Factor 4 general population exposure scores.

This choice of s_1, s_2, s_3, s_4, guaranteed that $\left|\frac{f_{ij}}{s_i}\right| \leq 1$ for all i and j, and furthermore, that for each i,

$$\left|\frac{f_{ij}}{s_i}\right| = 1$$

for at least one chemical j.

APPENDIX D

BIOLOCICAL AND ENVIRONMENTAL SCORES

A. The five human health effect factors and two environmental effect factors mentioned in the text were scored in the following manner:

Factor 1: Carcinogenicity

a. Numerical Scores Assigned:

3 Established carcinogen in humans or in 2 animal species, or in one animal species in well-replicated experiments

2 Established carcinogen in 1 animal species

1 Insufficient or inadequate experimental data for definite conclusions, but either (a) no experimental or structural reason for suspicion, or (b) good negative mutagenicity tests, or (c) low biological activity. (Note: some inert compounds -- examples, argon, nitrogen -- were given a score of zero on this factor despite not having been tested.

0 Adequately tested in animals with negative results in each of two species

b. Letter Scores Assigned*:

xxx Needs testing, strongly suspect (close structural relationship to known carcinogen, positive result in validated in vitro test, inconclusive but suspicious positive animal test, etc.)

xx Needs testing, suspect (structural resemblance to known carcinogen, etc.)

x Needs testing, some reason for suspicion (potent organ-specific toxin, enzyme inducer, suspect co-carcinogen, etc.)

*Chemicals presently undergoing testing for carcinogenicity in the framework of the NCI bioassay program were scored as suspect carcinogens. Their special status was documented for the members of the Committee.

c. Criteria for Accepting Positive Test Results (scores 2 or 3)

Validated positive findings in animal studies consisted of any test results which clearly indicated treatment-related carcinogenicity or tumorigenic effects. This was based on the criteria set out in the report of the National Cancer Advisory Board, Subcommittee on Environmental Carcinogenicity, "General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances (1976)".

d. Criteria for Accepting Negative Test Results (including zero scores)

In general, the protocol of the test conformed to, or was reasonably consistent with the current NCI Guidelines (J.M. Sontag et al., Guidelines for Carcinogen Bioassay in Small Rodents, DHEW 76-801). It was recognized that many older tests do not conform to these guidelines. Therefore, good scientific judgment was applied to the evaluation of these tests in order to determine whether differences in protocols significantly weakened confidence in the reported negative results. In assigning a zero score, the guiding principle was the judgment that further testing was unnecessary.

Factor 2; Mutagenicity

a. Numerical Scores Assigned:

2	Mutagen in two or more test systems*
1	Mutagen in one test system
0	Tested in more than one system with negative results and no reason for suspicion (similar to inactive compounds, etc.)

*These and other scores were normalized to the 0-3 scale or x-xxx scale respectively for all factors involved.

b. Letter Scores Assigned:

xxx	Needs testing, strong reason for suspicion (structural similarity to known mutagen, reported carcinogenicity, teratogenicity, or other cellular toxicity)
xx	Needs testing, some reason for suspicion (structural similarity to known mutagens and/or carcinogens)
x	Needs testing, no reason to assign high priority

c. Examples of Short-Term Test Systems Considered for Scoring Were:

The Salmonella/microsome test, (Ames), E. coli WP2 uvr A, etc. test (Bridges, Witkin), B. subtilis M45 Rec$^-$, etc. test (Kada), E. coli pol A+/pol A1- test (Rosenkranz), Yeast test (Zimmerman), Neurospora test (de Serres) and Drosophila test (Vogel). Mammalian cells in culture and in vitro transformations were also considered.

Factor 3: Teratogenicity

a. Numerical Scores Assigned:

3	Confirmed teratogen in humans or in two appropriate animal species
2	Confirmed teratogen in 1 animal species
1	Insufficient or inadequate experimental data for definite conclusions, but either (a) no experimental or structural reason for suspicion, or (b) low biological activity
0	Adequately tested in two suitable animal species with negative findings for teratogenic activity

b. Letter Scores Assigned:

xxx	Needs testing, strongly suspect (close structural relationship to known teratogen, inconclusive but suspicious positive animal tests, etc.)
xx	Needs testing, suspect (equivocal result in animal test, etc.)
x	Needs testing, some reason for suspicion

c. Criteria for Acceptance of Teratogenicity Tests

Accepted teratogenicity tests conformed reasonably to the recommendations and principles outlined in "Principles for Evaluating Chemicals in the Environment," National Academy of Sciences, pp. 173-182, 1975; and "The Testing of Chemicals for Carcinogenicity, Mutagenicity, Teratogenicity," Department of Health and Welfare, Canada, pp. 137-176, March 1973.

Factor 4: Acute Toxicity

a. Numerical Scores Assigned:

3	extremely toxic:	$<$ 50 mg/kg
2	very toxic:	50-500 mg/kg
1	moderately toxic:	0.5-5 g/kg
0	very slightly toxic:	$>$ 5 g/kg

b. Letter Scores Assigned:*

xx not tested, but suspected to be in range 2-3

x not tested, but suspected to be in range 0-1

*See factor 2 for normalized scored.

c. Criteria for Quantitation of Acute Toxicity

Standard systems of toxicity rating based on probably lethal dose in humans were used when available . Lowest lethal doses and LD50 values in various animal systems were also widely used.

Factor 5: Other Toxic Effects

a. Numerical Scores Assigned:

3 Effects at low doses (Guidelines: < 1 mg/kg/day)

2 Effects at moderate doses (Guidelines: 1-10 mg/kg/day)

1 Effects at high doses (Guidelines: >10 mg/kg/day)

0 Very low or negligible biological activity (e.g., nitrogen, argon, etc.)

b. Letter Scores Assigned:

xxx Needs testing (structural similarity to another chemical which rates 2 or 3; questionable reports of effects which need confirmation, etc.)

xx Needs testing, some reasons for suspicion

x Needs testing, inadequate information available to give high pirority

c. Criteria for Scoring

This factor includes both reversible and irreversible effects, delayed or cumulative toxicity, organ-specific effects, effects on reproduction, behavior, etc. The score entered reflects the toxic effects noted in animals (or in humans if data were available) at the lowest dose-range. If the chemical was reported or suspected to have more than one toxic effect, xxx or xx for one type of toxic effect superseded any numerical score for another. Also, x for one type of toxic effect superseded 2 or 1 for another. In many cases, reports of one type of effect at low doses engendered suspicion of the likelihood of others; in such cases the chemical was scored with the appropriate number of x's, unless thoroughly tested.

Factor 6: Bioaccumulation

a. Numerical Scores Assigned:

3 High ($>10^4$)*

2 Appreciable (10^2-10^4)

1 Low ($<10^2$)

0 Experimental evidence for non-accumulation (<1); water soluble compounds

*The degree of bioaccumulation (more precisely, the tissue-specific storage factor) is defined as the concentration of the chemical in the tissues (at "steady state" or after prolonged exposure) divided by the concentration of the chemical in the ambient medium.

b. Letter Scores Assigned:

xxx	Testing important, judged likely to be high
xx	Testing important, judged not likely to be high, but likely to be appreciable
x	Needs testing, little or no experimental data

c. Criteria for Scoring

Bioaccumulation is used here in its broad sense of the accumulation of a chemical in one or more tissues of an animal (or plant) to levels higher than those in the ambient medium. For purposes of screening chemicals, it was considered significant primarily in cases in which the accumulation in tissues represented an enhanced probability of effects, either on the organ in which the chemical was concentrated, or on animals which feed on the organism which accumulated the chemical. High degrees of bioaccumulation are usually found only in aquatic organisms. For these organisms, bioaccumulation is known to be dependent primarily on water solubility and it is empirically predicted by the octanol/water partition coefficient. Zero scores were assigned to completely water soluble organic chemicals.

Substances which are easily metabolized will not be bioaccumulated even if they have a high partition coefficient (example, chloroform). Thus ease of metabolism was a factor considered in evaluating the potential for bioaccumulation.

Factor 7: Ecological Effects

a. Numerical Scores Assigned:

3 Effects at low concentrations (10^{-9} or less in air or water)*

2 Effects at moderate concentrations (10^{-7} - 10^{-9} in air or water)

1 Effects at high concentrations (10^{-6} or greater in air or water)

0 No reported effects that could justify priority for testing

*In air for gases or vapors: 1 part of chemical per billion parts air by volume (ppb). In water for liquids and solids: 10^{-9} gram per cubic meter (ng/m^3)

b. Letter Scores Assigned:*

xx Testing needed, possibility of major or widespread effects

x Testing needed, possibility of minor or local effects

*See factor 2 for normalized scores.

c. Criteria for Scoring:

Ecological effects considered included beside toxic effects on non-human animals and plants, ecosystem effects, effects on atmosphere and climate, ozone depletion, etc. Generally, numerical scores (established hazard) were assigned only to a limited number of thoroughly tested chemicals (e.g., pesticides, some metal containing compounds, or some specific chemicals). In other cases, the potential for ecological effects was judged according to availability of data on toxicity in particular, published information on specific tests, structural similarity to compounds of better known eco-toxicity, published data on depletion potential for stratospheric ozone. Zero scores were assigned only to compounds with low biological activity (LD50 > 1 g/kg or AQTR > 100 ppm).

B. An extra factor was scored if the presence of a contaminant in a commercial product was the major reason for concern, or if a trace degradation product was the major reason for concern (examples: dioxin, methyl mercury).

Factor 8: Contaminants and Environmental Degradation or Conversion Products

a. Numerical or Letter Scores Assigned:

1 Contaminants, etc., known to be important

0 Contaminants, etc., not suspected, or known to be of no importance.

x Contaminants, etc., suspect, needs testing

b. Criteria for Scoring:

The scores for this factor were not averaged. A letter score took priority over a numerical score at any time; if no letter score was assigned to a chemical, the numerical score 1 was overriding. A zero score was assigned only if it was scored unanimously by all scorers. The score for this factor was not added: (1) if the principal breakdown product was the major problem and it was the basis for scores on other criteria such as persistence and toxicity (examples: DDE, PAN); (2) for in vivo metabolism of carcinogens to active forms (e.g., arene oxides, activated nitrosamines, etc. etc.).

C. It is of relevance for the scoring method to add that in order to facilitate the inclusion of a zero score in a letter score average, the zero score was changed into 0.1X. Also, in some instances fractional numerical or letter scores were assigned by scorers.

D. The following literature sources were extensively used by the scorers:

References of general interest

1. NIOSH Registry of Toxic Effects of Chemical Substances (1976)
2. Kirk-Othmer Encyclopedia of Chemical Technology. Edited by A. Standen, Interscience Publishers, New York (1963, 1972).
3. The Condensed Chemical Dictionary, 9th ed. Van Nostrand Reinhold Co., New York (1977).
4. The Merck Index, 9th ed. Merck & Co., Inc., Rahway, N.J. (1976).
5. Chemical Consumer Hazard Information System. Consumer Product Safety Commission, Washington, D.C. (1977).
6. A Study of Industrial Data on Candidate Chemicals for Testing. Stanford Research Institute, Palo Alto, California, (1976).

7. The Encyclopedia of Chemistry. Hanpel & Hawley, 3rd ed. Van Nostrand Reinhold Co., New York (1973).

8. Brown, S.L., et al. Research Program on Hazard Priority Ranking of Manufactured Chemicals, Phase II- Final Report to National Science Foundation. Stanford Research Institute Menlo Park, California (1975).

9. Dorigan, J., et al. Scoring of Organic Air Pollutants, Chemistry, Production and Toxicity of Selected Synthetic Organic Chemicals, MITRE, MTR-6248 (1976).

1. References on Carcinogenicity

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C2. Suspected Carcinogens - A subfile of the NIOSH Toxic Substances List.

C3. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Lyon, France. WHO, International Agency for Research on Cancer.

C4. Chemicals Being Tested for Carcinogenicity by the Bioassay Program, DCCP. National Cancer Institute (1977).

C5. Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity, No. 6. WHO, Lyon, France (1976).

2,3. References on Mutagenicity and Teratogenicity

MT1. Shepard, T.H. Catalog of Teratogenic Agents. Johns Hopkins University Press, Baltimore (1973).

MT2 EMIC/Environmental Mutagenicity Information Center File, National Laboratories, Oak Ridge, Tennessee.

4,5. References on Acute Toxicity and Other Toxic Effects

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A05. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1976. American Conference of Government Industrial Hygienists.

A06. Criteria for a Recommended Standard - Occupational Exposure to...., prepared by NIOSH..

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A09. Fairhall, L.T. Industrial Toxicology, 2nd. ed. Williams & Wilkins Co., Baltimore, Maryland (1969).

A010. Sax, N.I. Dangerous Properties of Industrial Materials, 3rd ed. Reinhold Publishing Corp., New York (1975).

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A012. Industrial Safety Data Sheets. National Safety Council, Chicago, Illinois.

6,7. References on Bioaccumulation and Ecological Effects

BE1. Applegate, V.C., J.H. Howell, A.E. Hall, Jr. & M.A. Smith, 1957 Toxicity of 4.346 Chemicals to Larval Lampreys and Fishes. U.S. Dept. Interior, Fish & Wildlife Service. Special Scientific Report-Fisheries No. 207. Wash., D.C.

BE2. Battelle Columbus Laboratories 1971, Effects of Chemicals on Aquatic Life: Selected Data from the Literature through 1968. Vol. 3 of Water Quality Criteria Data Book. U.S. Environmental Protection Agency, Washington, D.C.

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BE5. Leo, A., C. Hansch, & D. Elkins, Partition Coefficients and Their Uses. Chem. Rev. 71:525-616 (1971).

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INFORMATION DOSSIERS ON SUBSTANCES
DESIGNATED BY
TSCA INTERAGENCY TESTING COMMITTEE

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Washington, DC

A

Clement Associates, Inc.

Technical Support Team

Ian C.T. Nisbet, Ph.D., Project Director
Jay Turim, Ph.D., Project Manager

Morton Beroza, Ph.D.
Nan S. Gray
John F. Guy
Robert Katz, Ph.D.
Alfred E. Pinkney
Mukund J. Shah, Ph. D.
Barbara Turnham

The team acknowledges the assistance of a number of Clement's Associate Scientists and consultants during preparation of dossiers.

TABLE OF CONTENTS

Foreword D

Alkyl Epoxides I

Alkyl Phthalates II

Chlorinated Benzenes, Mono- and Di- III

Chlorinated Paraffins, 35-64% Chlorine IV

Chloromethane V

Cresols VI

Hexachloro-1,3-Butadiene VII

Nitrobenzene VIII

Toluene IX

Xylenes X

Appendices

General References Appendix A XI-1

Key to Abbreviations Appendix B XI-4

FOREWORD

This document has been prepared for the Toxic Substances Control Act (TSCA) Interagency Testing Committee by its technical contractor, Clement Associates, Inc. The Committee is charged with the responsibility for making recommendations to the Administrator of the Environmental Protection Agency (EPA) regarding chemical substances which should be given priority by EPA for testing to determine adverse effects on man or the environment.

The dossiers in this document were originally drafted by Clement and were reviewed in detail by the Committee, which in certain instances added additional information. Conclusions presented in the dossiers about specific studies were made by Clement scientists and were reviewed by the Committee. The information in the dossiers thus reflects the collective knowledge and judgment of the Committee and its technical contractor. It has been used as the primary basis for the designation of the chemicals involved for priority testing in the Committee's Initial Report to the Administrator, Environmental Protection Agency (Federal Register 42, 55026, October 12, 1977).

The dossiers were designed to provide the Committee with information on the chemicals' physical and chemical properties, exposure characteristics, and biological properties in sufficient detail to support an informed judgment on whether the substances could be given priority for testing. The dossiers are not comprehensive critical reviews. Such reviews could not be performed with the constraints imposed upon the Committee (and, therefore, the contractor) by the statutory deadlines of TSCA.

Faced with the task of preparing dossiers which could be quickly assembled and yet contain sufficient information for the Committee's purposes, Clement proceeded along the following lines.

Literature searches were conducted using the National Library of Medicine's TOXLINE and the Environmental Mutagen Information Center (EMIC) automated data banks. Each reference on a list of sources of general information (see General References - Appendix A) was reviewed. Further references and information were obtained from monographs, criteria documents, reviews, and reports available from government agency files and trade association libraries. Information received in response to the Committee's July 1977 Federal Register notice requesting information on certain substances was reviewed. Clement scientists relied upon their own knowledge of the literature to augment the data sources.

In general, secondary sources were consulted first in preparing the dossiers. When an article was judged to contain information of major significance or to require a critical review, the primary source was consulted. Except when specifically noted otherwise, the information cited in these dossiers was derived from the primary sources.

ALKYL EPOXIDES

TABLE OF CONTENTS

Page

Overview I-1

Part I - General Information

- Butane, 1,2:3,4-diepoxy stereoisomers I-3
- Ethane, 1,2-epoxy- I-5
- Butane, 1,2-epoxy- I-8
- Propane, 1,2-epoxy- I-10
- Summary of Characteristics I-12
- Specific References I-13

Part II - Biological Properties

- Butane, 1,2:3,4-diepoxy stereoisomers
  - 2.1 Bioaccumulation I-14
  - 2.2 Contaminants and Environmental Degradation or Conversion Products I-14
  - 2.3 Acute Toxicity I-14
  - 2.4 Other Toxic Effects I-16
  - 2.5 Carcinogenicity I-17
  - 2.6 Mutagenicity I-21
  - 2.7 Teratogenicity I-22
  - 2.8 Metabolic Information I-22
  - 2.9 Ecological Effects I-22
  - References I-23

Page

Part II - Biological Properties (Continued)

Ethane, 1,2-epoxy-

2.1 Bioaccumulation I-25

2.2 Contaminants and Environmental Degradation or Conversion Products I-25

2.3 Acute Toxicity I-26

2.4 Other Toxic Effects I-28

2.5 Carcinogenicity I-29

2.6 Mutagenicity I-31

2.7 Teratogenicity I-33

2.8 Metabolic Information I-34

2.9 Ecological Effects I-34

2.10 Current Testing I-34

References I-36

Propane, 1,2-epoxy-

2.1 Bioaccumulation I-39

2.2 Contaminants and Environmental Degradation or Conversion Products I-39

2.3 Acute Toxicity I-39

2.4 Other Toxic EFfects I-42

2.5 Carcinogenicity I-43

2.6 Mutagenicity I-43

2.7 Teratogenicity I-45

2.8 Metabolic Information I-45

2.9 Ecological Effects I-45

2.10 Current Testing I-45

References I-46

Page

Part III - Status of Carcinogenicity Studies on Epoxides at the National Cancer Institute I-47

Part IV - Information on Structural Analogs I-49

References I-52

ALKYL EPOXIDES

AN OVERVIEW

This category includes all noncyclic aliphatic hydrocarbons with one or more epoxy functional groups. Specific epoxides discussed in this dossier are diepoxybutane, ethylene oxide, butylene oxide and propylene oxide. Diepoxy butane, butylene oxide and propylene oxide are colorless liquids and ethylene oxide is a colorless gas. All are soluble in water and common organic solvents.

Several alkyl epoxides are produced in very large quantities (e.g., annual production of ethylene oxide exceeded 4 billion pounds and propylene oxide exceeded 1.8 billion pounds in 1976). These compounds are used as intermediates in the manufacture of industrial chemicals such as ethylene glycol, and propylene glycol. Ethylene oxide may be present in several consumer products, including paint strippers and detergents and is used in medical facilities for sterilization of heat-sensitive materials.

It is estimated that 100 million pounds of ethylene oxide and over 40 million pounds of propylene oxide are annually released into the environment. Occupationally, about 165,000 workers are estimated to be exposed to the former compound and 264,000 workers to the latter. Another 105,000 workers are estimated to be exposed to butylene oxide.

These compounds do not accumulate in animal tissue, nor do they persist appreciably in the environment. However, one of their reaction products, ethylene chlorohydrin, may be of potential concern. Little information was found on the ecological effects of the alkyl epoxides.

Diepoxides are reported to be carcinogenic in animal studies. No carcinogenic effect has been observed for ethylene oxide while propylene oxide is reported to be carcinogenic in rats. Epoxides are reported to be mutagenic in several test systems. Teratogenicity data on epoxides are not available in the literature.

ALKYL EPOXIDES

PART I

GENERAL INFORMATION

I. Butane, 1,2:3,4-diepoxy stereoisomers (including (+-)-1,2:3,4-diepoxy butane and meso-1,2:3,4-diepoxy butane)

1.1 Identification

		CAS #	NIOSH #
A.	Butane, 1,2:3,4-diepoxy-	001464535	EJ82250
B.	Butane, (+-)-1,2:3,4-diepoxy-	000298180	EJ84000
C.	Butane, meso-1,2:3,4-diepoxy-	000564001	EJ87500

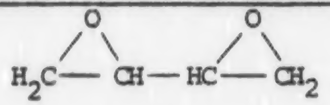
1.2 Synonyms and Trade Names

A. 1,1'-Bi(ethylene)oxide; bioxiran; bioxirane; butadiene diepoxide; butadiene dioxide; 1,2:3,4-diepoxybutane; threitol, 1,2:3,4-dianhydro-; 2,2'-dioxirane; erythritol anhydride; 2,4-diepoxybutane; dioxybutadiene (G9,G16,G23)

B. dl-Butadiene dioxide; dl-1,2:3,4-diepoxy butane; bioxirane; (R*,R*)-(+-)-2,2'-bioxirane; 1,2:3,4-dianhydro-dl-threitol (G9,G16,G22)

C. meso-diepoxybutane; meso-1,2:3,4-diepoxybutane; erythritol anhydride; 1,2:3,4-dianhydro-erythritol; (R*,S*)-2,2'-bioxirane (G9,G16,G23)

1.3 Chemical Formual and Molecular Weight



$\overset{O}{H_2C-CH}-\overset{O}{HC-CH_2}$

$C_4H_6O_2$ Mol. wt. 86.09

(G16,G23)

1.4 Chemical and Physical Properties

1.4.1 **Description:** Colorless liquid (G9,G23)

1.4.2 **Boiling Point:** 138-144° C (G22)

1.4.3 **Melting Point:**
A. No information found in sources searched
B. 4° C (G22)
C. -16° C (G22)

1.4.4 Absorption Spectrometry: IR epoxide band at 1250 cm^{-1} (G9)

1.4.5 Vapor Pressure:

No information found in sources searched

1.4.6 Solubility: Soluble in alcohol and water (G23,G22)

1.4.7 Octanol/Water Partition Coefficient:

No information found in sources searched

1.5 Production and Use

1.5.1 Production:

No information found in sources searched

1.5.2 Use: In curing polymers; for crosslinking textile fibers; to prevent microbial spoilage (G23)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure:

No information found in sources searched

1.7 Manufacturers

No information found in sources searched

ALKYL EPOXIDES

II. Ethane, 1,2-epoxy —

1.1 Identification

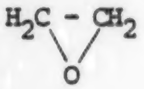
CAS No.: 000075218
NIOSH No.: KX24500

1.2 Synonyms and Trade Names

Ethylene oxide; Anprolene; dihydrooxirene; dimethylene oxide; E.O.; E.T.O.; oxacyclopropane; oxane; oxidoethane; alpha, beta, oxido ethane; oxiran; oxirane; di-hydro oxirene

(G16)

1.3 Chemical Formula and Molecular Weight



C_2H_4O Mol. Wt. 44.05

(G16,G22)

1.4 Chemical and Physical Properties

1.4.1 Description: Colorless, flammable gas at ordinary room temperature and pressure; colorless mobile flammable liquid below 12°C; reduces $AgNO_3$; reacts with active hydrogen compounds and with inorganic chloride in foods to form ethylene chlorohydrin

(G9,G23,G25)

1.4.2 Boiling Point: 10.7° C (G23)

1.4.3 Melting Point: -111° C (G22)

1.4.4 Absorption Spectrometry:

$$\lambda_{max}^{gas} = 169, 171 \text{ nm}$$

$$\log \epsilon = 3.58, 3.57$$ (G22)

1.4.5 Vapor Pressure: 400 mm at -4.9° C

1.4.6 Solubility: Soluble in water, alcohol, ether, acetone and benzene

(G22)

1.4.7 Octanol/Water Partition Coefficient:

$$\text{Log } P_{oct} = 0.30$$ (5)

1.5 Production and Use

1.5.1 **Production:**
3,961.800 Million lbs (1972)
4,466.854 Million lbs (1975)
4,184.258 Million lbs (1976) (G24)

1.5.2 **Use:** As a fumigant for foodstuffs and textiles; to sterilize surgical instruments and medical materials; as an agricultural fungicide; in organic syntheses, esp. in the production of ethylene glycol; as starting material for the manufacture of nonionic surfactants

(G23)

Quantitative Distribution of Uses:

	Percent
Ethylene glycol (for antifreeze)	27
Ethylene glycol (for polyester)	23
Ethylene glycol (miscellaneous)	10
Surface-active agents	13
Ethanolamines	9
Miscellaneous	18
	100

(G25)

Consumer Product Information:

Ethylene oxide is present in:

commerical gas sterilizing agents;
aluminum brighteners;
paint stripper;
detergent;
polymer in denture adhesive

(G35)

1.6 Exposure Estimates

1.6.1 **Release Rate:** 98.8 Million lbs (G28)

1.6.2 **NOHS Occupational Exposure:**

Rank: 773

Estimated no. of persons exposed: 165,000*

*rough estimate (G29)

1.7 Manufacturers

BASF Wyandotte Corp.
Calcasieu Chemical Corp.
Celanese Chemical Co.
Dow Chemical Co.
Houston Chemical Co.
Jefferson Chemical Co.
Koch Chemical Co.
Northern Petroleum Co.
Olin Corp.
Shell Chemical Co.
Sun Olin Chemical Co.
Texas Eastman Co.
Union Carbide Corp.

(G25)

ALKYL EPOXIDES

III. Butane, 1,2-epoxy-

1.1 Identification

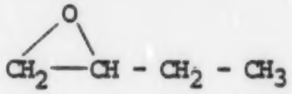
CAS No.: 000106887
NIOSH No.: EK36750

1.2 Synonyms and Trade Names

Butylene oxide; butane, 1,2-epoxy; 1-butene oxide; 1,2-butene oxide; ethylene oxide, ethyl; 1,2-butylene oxide

(G16)

1.3 Chemical Formula and Molecular Weight



C_4H_8O Mol. wt. 72.12

(G21,G22)

1.4 Chemical and Physical Properties

1.4.1 **Description:** Colorless liquid, highly flammable

(G21)

1.4.2 **Boiling Point:** 63.3° C (G22)

1.4.3 **Melting Point:** -150° C (G21)

1.4.4 **Absorption Spectrometry:**

No information found in sources searched

1.4.5 **Vapor Pressure:**

No information found in sources searched

1.4.6 **Solubility:**

Decomposes in hot water;
Soluble in water;
Very soluble in alcohol, acetone, and organic solvents;
Soluble in all proportions in ether

(G21,G22)

1.4.7 **Octanol/Water Partition Coefficient:**

No information found in sources searched

1.5 Production and Use

1.5.1 Production:

9 million lbs (estimate) (1974) (6)

1.5.2 Use:

As an intermediate for polymers; used in combination with amines to stabilize trichloro- and tetrachloroethylene; used as a fuel additive to prevent carburetor icing and improve antiknock properties (G21,1,2,3)

1.6 Exposure Estimates

1.6.1 Release Rate:

~ 7 Million lbs (7)

1.6.2 NOHS Occupational Exposure:

Rank: 1106

Estimated no. of persons exposed: 105,000*

*rough estimate (G29)

1.7 Manufacturers

Dow Chemical Company
Story Chemical Corp., Farchan Division
(G24,4)

ALKYL EPOXIDES

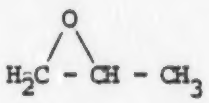
IV. Propane, 1,2-epoxy-(dl)

1.1 Identification CAS No.: 000075569
NIOSH No.: TZ29750

1.2 Synonyms and Trade Names

Epoxypropane; 1,2-epoxypropane; ethylene oxide, methyl; methyl oxirane; propene oxide; 1,2-propylene oxide; methyl oxiran
(G16,G22)

1.3 Chemical Formula and Molecular Weight



C_3H_6O Mol. wt. 58.08
(G16,G22)

1.4 Chemical and Physical Properties

1.4.1 Description: Colorless liquid, ethereal odor, extremely flammable
(G23)

1.4.2 Boiling Point: 34.3° C (G22)

1.4.3 Melting Point: -112.13° C (G23)

1.4.4 Absorption Spectrometry:

No information found in sources searched

1.4.5 Vapor Pressure: 400 mm at 17.8° C (G22)

1.4.6 Solubility: Soluble in all proportions in water, alcohol and ether
(G22)

1.4.7 Octanol/Water Partition Coefficient:

$\text{Log } P_{oct} = 0.13$ (5)

1.5 Production and Use

1.5.1 Production:

1,640.00 Million lbs (1972)
1,523.613 Million lbs (1975)
1,823.222 Million lbs (1976) (G24)

1.5.2 Use:

As a chemical intermediate in preparation of polyethers to form polyurethanes; used in preparation of propylene and dipropylene glycols; used in preparation of lubricants, surfactants, oil emulsifiers; as a solvent, fumigant, soil sterilant

(G23)

Quantitative Distribution of Uses:

	Percent
Polypropylene glycol and polyester glycols for urethanes	56
Propylene glycol	29
Dipropylene glycol	5
Surfactants	5
Glycol ethers and miscellaneous	5
	100

(G25)

1.6 Exposure Estimates

1.6.1 Release Rate:

40.8 Million lbs (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 582

Estimated no. of persons exposed: 264,000*

*rough estimate (G29)

1.7 Manufacturers

BASF Wyandotte Corp.
Dow Chemical USA
Jefferson Chemical Co., Inc.
Olin Corp.
Oxirane Chemical Co.
Celanese Corp.
Calcasieu Chemical Corp.
Texas Eastman Co.
Northern Petrochemicals Co.
Premier Petrochemical Co.
Shell Oil Co.
Sunolin Chemical Co.
Union Carbide Corp. (G24)

SUMMARY OF CHARACTERISTICS

ALKYL EPOXIDES

Name	Solubility	Log P_{oct}	Estimated Environmental Release (Million lbs)	Production (Million lbs)	Estimated no. of persons exposed (Occupational)	Use
Butane, 1,2:3,4-diepoxy stereoisomers	s in H_2O and alc	*	*	*	*	In curing polymers; for crosslinking textile fibers; to prevent microbial spoilage
Ethane, 1,2-epoxy-	s in H_2O, alc, eth, ace, bz	-0.30	98.8	3,961.800 (1972) 4,466.854 (1975) 4,184.258 (1976)	~165,000	In mfg. of ethylene glycol (in anti freeze, in plastics and fibers), surfactants, ethanolamines
Butane, 1,2-epoxy-	s in H_2O; vs in alc, ace, os. ∞ in eth	*	*	9. (1974)	~105,000	Stabilizer for chlorinated solvents (trichloro- and tetrachloro- ethylene) fuel additive
Propane, 1,2-epoxy- (dl)	∞ in H_2O, alc and eth	0.13	40.8	1,640.00 (1972) 1,523.613 (1975) 1,823.222 (1976)	~264,000	Mfg. of polyethers to form polyurethanes; mfg. of propylene glycols

* No information found in sources searched.

SPECIFIC REFERENCES FOR PART I

1. Dial, W.R., Stabilization of liquid halogenated aliphatic hydrocarbons- Pittsburgh Plate Glass Co. U.S. Patent 3,250,331 March 13, 1962.
2. Copelin, H.B. Stabilization of chlorinated Hydrocarbons - E.I Dupont de Nemours and Co. Patent 2,797,250 June 25, 1957.
3. Thomas, C.L. Motor Fuel anti-icing additives U.S. Patent 2,857,254 October 21, 1958.
4. Chemical Week Buyers Guide, 1977.
5. EPA, Office of Toxic Substances. Review of the enivronmental fate of selected chemicals. Task 3, Final report, Contract No. 68-01-2681, May, 1977.
6. Chemical Selection of Subgroup Clearinghouse on Environmental carcinogens. National Cancer Institute (November 1977).
7. Personal Communication with Warren Piver (November, 1977).

ALKYL EPOXIDES

Butane, 1,2:3,4-Diepoxy

Butane, (+ -)-1,2:3,4-Diepoxy

Butane, 1,2:3,4-Diepoxy, Meso

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

These compounds are soluble in water and react with water, where they are hydrolyzed to more water-soluble compounds. Thus, they are unlikely to bioaccumulate.

2.2 Contaminants and Environmental Degradation or Conversion Products

Diepoxybutane preparation involves reaction of 1,4-dichloro-2,3-butanediol or a 2,3-dihalogeno-1,4-butanediol compound with sodium hydroxide. The DL-form has been prepared from 1,4-dibromo-2-butene and the meso-form from 1,4-dihydroxy-2-butene or 3,4-epoxy-1-butene (G9). Diepoxybutane is slowly hydrolyzed in water to erythritol or threitol (G9). The starting materials outlined above may be contaminants in the final product; however no published data on technical products and impurities were available in the literature.

2.3 Acute Toxicity

The NIOSH Registry of Toxic Effects of Chemical Substances (G16) reports the acute toxicity of diepoxy butane as follows:

Butane, 1,2:3,4-Diepoxy

Parameter	Dosage	Animal	Route
LD50	78 mg/kg	rat	oral
LC50	90 ppm/4hr	rat	inhalation
LD50	72 mg/kg	mouse	oral
LD50	89 mg/kg	rabbit	skin

Butane, (+ -)-1,2:3-4-Diepoxy

LD50	210 mg/kg	rat	oral
LC50	56 ppm/4hr	rat	inhalation
LDLo	400 mg/kg	mouse	skin
LD50	800 mg/kg	rabbit	skin

Butane, 1,2:3,4-Diepoxy-, Meso-

LDLo	400 mg/kg	mouse	skin
LD50	25 mg/kg	mouse	intraperitoneal

Smyth et al. (1) reported the following data on mixed stereoisomers of diepoxybutane.

LD50	78 mg/kg	rat	oral
LD50	89 ml/kg	rabbit	skin

0.01 ml. of undiluted diepoxybutane caused primary skin irritation (necrosis) on the clipped skin of rabbits within 24 hours of application (1).

Inhalation of concentrated vapors in air killed all of 6 rats within 15 minutes (1).

The LC50 for a 4-hour exposure to rats is 90 ppm. Lachrymation, clouding of the cornea, labored breathing, and congestion of the lung occurs. Survivors have atrophy of the thymus, involution of the spleen, and decreased weight gain during the recovery period (G38).

Diepoxybutane has been reported to cause chemical eye injury. Smyth reported (1) severe burn, corneal necrosis eye injury in rabbits from 0.5 ml of a 10% solution in water or propylene glycol.

Five minute exposure to 10 ppm caused pronounced nasal and eye irritation, whereas 5 ppm was tolerated (G38).

2.4 Other Toxic Effects

Skin applications repeated 3 times weekly for 1 year caused consistent sebaceous gland suppression, intense hyperkeratosis and marked hyperplasia. Following six intramuscular administrations of 25 mg/kg to rats, leukopenia and relative lymphopenia occur (G38).

During carcinogenicity testing by lifetime skin application on mice, Van Duuren *et al*. (2) reported the following skin irritation effects of two isomers of 1,2:3,4-diepoxybutane.

Compound	Concentration (% in acetone)	Skin Irritation
D,L-	10 and 3	Severe hair loss, crusting and/or scarring persisting throughout experiment.
Meso	10 and 3	Hair loss and crusting persisting for 3 months or more, recurring 2 or more times during the experiment.

Diepoxybutane was locally narcotizing to tissues and caused extreme irritation of the pulmonary tract. It has pronounced radiomimetic effects (growth inhibitory, mutagenic and cytotoxic activity) (G38).

In man, minor accidental exposures to mixed stereoisomers have caused swelling of the eyelids and eye, and upper respiratory tract irritation within 6 hours (G38).

2.5 Carcinogenicity

Diepoxides are more frequently carcinogenic than monofunctional epoxides (3). Carcinogenicity data on diepoxybutane has been reported in two secondary sources, PHS-149 (G18) and an IARC monograph (G9, Vol. 11). Van Duuren *et al*. have published a series of articles (2-5) on the carcinogenicity of diepoxybutane. IARC (G9) evaluated the animal data on diepoxybutane as follows:

> "D-L- and meso-1,2:3,4-diepoxybutane are carcinogenic in mice by skin application: both compounds produced squamous-cell skin carcinomas. The D,L-racemate also produced local sarcomas in mice and rats by subcutaneous injection. L-1,2:3,4-Diepoxybutane is carcinogenic in mice by intraperitoneal injection."

Results of earlier experiments (6) on the carcinogenicity of the diepoxybutanes were inconclusive because of the low survival rate of the mice. One malignant tumor was observed in the group receiving the D,L-isomer. Only 4 animals survived for longer than 8 months and after 12 months there were no survivors. In the group receiving the meso-isomer, 10 animals survived more than 8 months and 4 malignant tumors were observed (4). The later studies (2, see Table 1) lead to the conclusions that both sterioisomers are clearly carcinogenic and that the D,L-isomer is a more active carcinogen and also more toxic than the meso-isomer. D,L- and meso-diepoxybutane gave both benign and malignant tumors.

Table 1

Effects of Skin Painting of Diepoxybutanes on Mice (2)*

Compound	Concentration (% in acetone)	Median Survival Time (days)	Cumulative No. of mice with Papilloma	Cumulative No. of mice with Carcinoma
D,L.	10	165	1	0
	3	475	10	6
Meso	10	357	5	4
	3	491	1	0

*30 mice per group. Papillomas include animals which developed only one or more benign tumors. Animals that have one or more squamous epidermial carcinomas are counted under the column titled "carcinoma".

D,L-diepoxybutane is carcinogenic to mouse skin but does not induce gastric cancers in rats. This finding is related to the rapid acid-catalyzed hydrolysis of epoxides in the rat stomach. It induced tumors mainly at the site of application and did not give any significant incidence of tumors at sites distant from the site of application. Connective tissue of rats is not usually sensitive to tumor induction by these compounds (3).

In a carcinogenicity study of 1,2:3,4-diepoxybutane by skin painting 20 mice (strain 57Bl) were given a total dose of 1 mMole of the compound (duration of experiment not specified). The first tumor appeared at 5 months, with all 20 animals having survived to this period. Seven developed skin tumors and two developed malignant lymphomas (G18,7).

Experimental protocols and tumorigenic data from carcinogenicity studies of diepoxybutane by skin application and subcutaneous injection are shown in Tables 2 to 4.

Table 2

Carcinogenicity Study of Diepoxybutane by Skin Application

Compound	Animal	Route of Exposure	Median Survival Time	Tumorigenic Effects
meso-1,2:3,4-Diepoxybutane	30 mice	skin applications on the clipped dorsal skin 10 mg/animal in 0.1 ml acetone 3 times weekly	154 days	6/30 squamous papilloma
D,L-1,2:3,4-Diepoxybutane	30 mice	same as above	78 days	2/30 squamous papillomas 1/30 squamous-cell carcinoma
Control (Solvent)	90 mice	same as above	235 days	8/90 squamous papillomas

(Reference: G9, G18, 4)

Table 3

Carcinogenicity Study of Diepoxybutane by Skin Application

Compound	Animal	Route of Exposure	Median Survival Time	Tumorigenic Effects
D,L-1,2:3,4-Diepoxybutane	30 mice	3 and 10 mg in 0.1 ml acetone skin application on the clipped dorsal skin, 3 times weekly for lifespan	165 days for high dosage (10 mg)	1/30 - skin papilloma (at 10 mg dose) 10/30 skin papilloma 6/30 squamous-cell carcinoma (at 3 mg dose)

Table 3 (continued)

meso-1,2:3,4-Diepoxybutane	30 mice	same as above	357 days for high dosage (10 mg)	5/30 skin papilloma 4/30 squamous-cell carcinoma (at 10 mg dose)
				1/30 skin papilloma 0/30 carcinoma (at 3 mg dose)
Control (acetone)	60 mice	same as above	447 days	No skin tumor

(Reference: G9, G18, 2)

Table 4

Subcutaneous Injection[1] of D,L-1,2:3,4-diepoxybutane

Animal	Dose, mg in 0.05 ml Tricaprylin	Number of Animals	Median Survival Time (days)	Duration of Test (days)	Tumors at Injection Site
mice	0.1	50	456	489	2 Adenocarcinomas[2] 5 Fibrosarcomas
mice	1.1	30	328	401	5 Fibrosarcomas
rat	1	50	471	550	1 Adenocarcinoma 9 Fibrosarcomas

Solvent-treated control mice developed no tumors at injection site. Distant tumors were not numerically significant.

[1] once weekly over the specified time

[2] all adenocarcinomas were of breast origin

(Reference: G9, G18, 3)

2.6 Mutagenicity

The mutagenicity of the individual stereoisomers of diepoxybutane has been tested only in plants.

Mixed stereoisomers have been reported in an IARC monograph (G9, Vol. 11) to be mutagenic in a number of microbial, insect, and human studies, as follows.

a) Prophage induction in *Bacillus megaterium* and *Pseudomonas pyocyanea* (8) and in *Escherichia coli* k-12 (9).

b) Reverse mutation induced in strain TA 1535 of *Salmonella typhimurium* (10), in *Schizosaccharomyces pombe* (11) and in B and B/r strains of *Escherichia coli* (12), after treatment for 1 hour at 37°C with 0.01 M and 0.02 M aqueous solutions, respectively.

c) Reverse mutations induced in the purple, adenine-requiring mutant 38701 of *Neurospora crassa* after treatment with a 0.2 M solution (13).

d) Mitotic gene conversions were produced in strain D4 of *Saccharomyces cerevisiae* (14-15), after 5 hours of treatment with a 0.005 M solution.

e) Sex-linked recessive lethal mutations, visible mutations, semi-lethal mutations, and translocations were produced in *Drosophilia melanogaster* (16-19).

f) Chromosome aberrations were found in cells taken from a patient suffering from Franconi's anaemia after treating the cells *in vitro* with diepoxybutane (20).

Bianchi and Cotin (21) have reported that diepoxybutane is a chemical mutagen in maize pollen but the capacity to affect the hereditary material differs depending on the specific isomer employed. The L-form is the most effective followed by D and meso forms. Also, the racemic solution shows more or less pronounced synergism.

2.7 Teratogenicity

No information was found in searched literature.

2.8 Metabolic Information

Epoxides have been found to undergo rapid acid-catalyzed hydrolysis in the rat stomach (3). Diepoxybutanes are hydrolyzed to erythritol, a naturally occurring sugar, when mixed with water (G23).

2.9 Ecological Effects

No information was found in sources searched.

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ETHYLENE OXIDE

(Ethane, 1,2-epoxy)

2.1 Bioaccumulation

Ethylene oxide is readily soluble in water and has a log P_{oct} value of -0.30. Therefore this compound is not believed to accumulate in animal tissues (1). Since ethylene oxide has such a high vapor pressure, one would not expect to find it in the aquatic environment.

2.2 Contaminants and Environmental Degradation or Conversion Products

An IARC monograph (G9, Vol. 11) has reported the following information on technical products and impurities of ethylene oxide from the EPA Compendium of Registered Pesticides (2). Ethylene oxide is available in technical and pure (99.7%) grades. A typical technical grade product contains water (0.03%), acetaldehyde (0.01%), acetic acid (0.002%), non-volatile residue (0.1g/1). Ethylene oxide is also available as a 10-80% pressurized or liquified gas formulated with carbon dioxide, trichlorofluoromethane or dichlorodifluoromethane to reduce fire hazards. In one study (3), 2.3% air and 0.7% acetylene by weight have been reported as the only impurities in 97.0%-98.6% commercial grade ethylene oxide. Ethylene oxide production involves direct catalytic oxidation of ethylene with air or oxygen (G9, Vol. 11). The starting materials may possibly add contaminants.

Ethylene oxide is a volatile polar compound which is moderately reactive toward a variety of nucleophilic species, including water, via acid, base and neutral reactions (1). It is rapidly hydrolyzed ($t_{1/2}$=2.5 days in neutral solutions) (G14,G15). If dispersed into the atmosphere, ethylene oxide will be oxidized by hydroxy radical with a half life of one to six days. However, it is extremely unreactive towards peroxides and ozone (G14,G15). The biochemical oxygen demand (BOD) is reported to be 31% of theoretical after 10 days at 70° F at 100 mg/ml. Total theoretical oxygen demand is 1.82 gm/gm (G15).

After sterilization and fumigation of various organic materials and synthetic objects with ethylene oxide, residues of ethylene oxide, ethylene chlorohydrin and ethylene glycol are found (35).

2.3 Acute Toxicity

The NIOSH Registry of Toxic Effects of Chemical Substances (G16) reports the acute toxicity of ethylene oxide as follows:

Parameter	Dosage	Animal	Route
LD50	330 mg/kg	rat	oral
LC50	1462 ppm/4hr	rat	inhalation
LC50	836 ppm/4hr	mouse	inhalation
LC50	960 ppm/4hr	dog	inhalation
LD50	270 mg/kg	guinea pig	oral
LCLo	7000 ppm/150 min	guinea pig	inhalation

Hollingsworth et al. (3) have reviewed the toxicity of ethylene oxide. Major toxic effects and sources cited in this article are as follows:

Exposure to 50,000 to 100,000 ppm causes death in guinea pigs after a few minutes. Exposure to 3000 to 6000 ppm for 30 to 60 minutes is dangerous to the life of guinea pigs; 3000 ppm is the maximum amount for 60 minutes and 250 ppm is the maximum concentration that can be tolerated for several hours by guinea pigs without serious disturbances (4).

Less extensive studies on acute inhalation toxicity of ethylene oxide for various animal species have been cited (5-24) by Hollingsworth et al. (3).

Ethylene oxide is an irritant, a central nervous system depressant, and a protoplasmic poison. Deaths due to respiratory paralysis may result promptly from single vapor exposures causing deep anesthesia when animals are exposed once to lower concentrations of ethylene oxide vapor; delayed deaths may occur due to lung edema, secondary respiratory infection and/or kidney and liver injury. Symptoms of excessive exposure observed in animals include irritation of the eyes, nose, and throat; vomiting; weakness; tremors; and shortness of breath.

After exposure of dogs, cats, rabbits, guinea pigs, rats and mice to ethylene oxide vapor (concentrations greater than 1000 ppm for 2 hours), some cats exhibited salivation and lacrimation, dogs vomited occasionally, and breathing was somewhat accelerated in all animals. Following removal of the animals from the exposure, corneal opacity was seen, especially in the guinea pigs. Transient fits of coughing and nausea were observed in the dogs and cats. The animals that survived the more severe exposures (concentrations of 250 to 4000 ppm and exposures times of 1 to 48 hours) appeared to recover completely, but showed delayed effects of apathy, dyspnea, inflammation of the periosteum, paralysis of the hind legs, severe respiratory distress, periodic convulsions and deaths. Autopsy of the animals revealed congestion, hyperemia and emphysema of the lungs; plethora, congestion, and fatty degeneration of the liver; cloudy swelling of the tubules of the kidneys; infrequent fatty degeneration of the muscle fibers and of the media of the coronary blood vessels of the heart; and plethora of the spleen and brain (5).

Early symptoms of excessive acute vapor exposure of humans to ethylene oxide alone or in an admixture with carbon dioxide are irritation of the eyes, nose, and throat. Symptoms of nausea, vomiting, headache, shortness of breath, cyanosis, diarrhea, mental dullness, drowsiness, weakness, incoordination, pulmonary edema, electrocardiogram abnormalities, lymphocytosis, and urinary excretion of bile pigments appear later (15-23).

Pure anhydrous liquid ethylene oxide does not cause primary injury to the dry skin of man, but rapid vaporization on the skin results in a freezing reaction of the skin (24).

Prolonged, intimate skin contact with dilute or concentrated aqueous solutions of ethylene oxide can cause severe delayed burns. After a latent period of several hours, the concentrated solutions produced edema and erythema. Shortly thereafter, vesiculation and/or impressive bleb formation were observed in the cases of all aqueous solutions contacted. Nausea and vomiting were observed when a 1% solution of ethylene oxide in water had direct contact with skin for about two hours (23,24).

2.4 Other Toxic Effects

Hollingsworth et al. (3) have reported the effects of repeated exposure to ethylene oxide as follows:

When animals were subjected to repeated seven-hour exposures of ethylene oxide vapor, five days a week, for six or seven months, guinea pigs, rabbits, and monkeys tolerated 113 ppm and rats and mice tolerated 49 ppm without adverse effects. Repeated oral doses of 0.03 g/kg of ethylene oxide given daily, 5 days a week, for a period of 30 days produced no toxic effects in rats.

Irritation of the respiratory passage and injury to the lungs occurred when animals were exposed repeatedly to 204, 357 and 841 ppm of ethylene oxide vapor for seven hours a day, five days a week during a period of 182 days. Secondary respiratory infection caused the deaths of an appreciable number of rats and mice under these circumstances. Injury to the liver, kidneys, adrenals and testes was noted in the rats and guinea pigs. Delayed reversible effects, characterized by impairment of function (both sensory and motor) of the nervous system at the level of the lumbar and sacral region occurred. Paralysis, muscular atrophy of the hind limbs and growth depression and organ weight changes were observed in rats, rabbits and monkeys.

The Threshold Limit Value (TLV) recommended by ACGIH is 50 ppm (approximately 90 mg/m^3) (G11).

2.5 Carcinogenicity

Carcinogenicity studies have been reported in the Public Health Service Survey (G18, Vol. II-#829 and Vol. 1961-67-#1203) and in an IARC monograph (G9, Vol 11) as follows:

In limited studies, no carcinogenic effects were found when ethylene oxide was tested in mice by skin application in rats by subcutaneous injection and in dogs, rats and mice by inhalation. The experimental details are outlined below.

Skin Application:

Thirty mice were painted three times weekly on the clipped dorsal skin with ethylene oxide (0.1 ml. of a 10% solution in acetone) for life. The median survival times was reported in IARC (G9) to be 493 days (25).

Subcutaneous Administration:

Twelve rats received maximum total doses of 1g/kg ethylene oxide in arachis oil by subcutaneous injection for 94 days. The animals were observed for lifetime; no local sarcomas were reported (26, as cited in G9).

Inhalation Study:

Three dogs (beagle), 30 mice and 20 rats were exposed to different concentration levels of ethylene oxide from 6 weeks to a maximum of 6 months. The survival rate was very low in mice (35, as reported in G18).

Other Experimental System:

Positive results have been reported in mice exposed to shredded corn cob bedding treated with ethylene oxide 150 days and then to untreated bedding for the rest of the life span (maximal, 900 days). Sixty-three out of 86 mice developed tumors at various sites. No tumors were reported in female mice which were not exposed to treated bedding (27, as cited in G9).

The IARC working group (1975-76) on the evaluation of the carcinogenic risk of chemicals to man comments on the above positive data that "This observation does not allow an evaluation of the carcinogenicity of ethylene oxide"; and on the negative data that "Although no carcinogenic effect was observed, the data do not allow an evaluation." No case reports or epidemiological studies were available to the working group (G9, Vol. 11).

2.6 Mutagenicity

Information on the mutagenicity of ethylene oxide has been compiled from two secondary sources: an IARC monograph (G9, Vol. 11) and an EPA report (G28). Evaluation of the test results of these studies has been provided in the latter source as follows:

Positive Tests Reviewed

Treatment with 9.55 mM ethanol solution of ethylene oxide for one hour at 25°C produced reverse mutations in *Salmonella typhimurium* strain TA1535 (28).

Treatment with a 0.025 M aqueous solution for 15 minutes produced reverse mutations in the adenine-requiring mutant strain 38701 of *Neurospora crassa* (29).

Ethylene oxide was found to be weakly active in the induction of sex-linked recessive lethal mutations and translocations in *D. melanogaster*. The chemical was administered to males by injection in single doses of a 0.055 or 0.09 M saline solution. This result was confirmed in another study. The chemical was also found to be active in inducing minute mutants (small chromosome deletions resulting in reduction of length and thickness of bristles) in *D. melanogaster* (30-32).

Negative/Inadequate Tests Reviewed

Ethylene oxide produced dominant lethal mutations in rats exposed for 4 hours to 1.83 g/m^3 (1000 ppm) (33). Chromosome aberrations were induced in bone marrow cells of rats exposed by inhalation to 0.45 g/m^3 (250 ppm) ethylene oxide for 7 hours per day for 3 days (33). In both experiments the presented data was judged to be inadequate for evaluation (G28).

Unreviewed Tests

Ethylene oxide has been reported to be inactive in the induction of reversions to methionine and glutamate prototrophy in *Streptomyces griseoflavus*, weakly active in inducing prophage in *Escherichia coli*, and inactive in inducing host-range mutations in bacteriophage T2h+ and the parent bacteriophage T2. These tests were not reviewed because the mutational events occurring have not been adequately characterized as screens for genetic damage (G28).

Studies with Insufficient Data for Evaluation or Not Reviewed

Administered by inhalation at a single dose level of 1000 ppm for four hours, ethylene oxide induced dominant lethal mutations in germ cells of male Long-Evans rats (G28).

Ethylene oxide has also been reported to be mutagenic in several plant systems. Chromosome breaks, breviaristatum mutants, eceriferum mutants, and chlorophyll mutants were observed in sprouts of barley seeds treated with ethylene oxide. Mutations were observed in wheat (*Triticum aestivum* var. *vulgare*) after treatment of the seeds with ethylene oxide. Chromosome aberrations were detected in germinating seedlings of *Pterotheca falconera* treated with the chemical and recessive mutations were detected in *Eucalyptus* species *tereticornis*, *citriodoro*, and *malculata* two generations after treatment of seedlings. Chromosome aberrations (e.g., chromatic breaks) were found in pollen grains of *Tradescantia paludosa* and in root tips of *Vicia faba* exposed to ethylene oxide. Chlorophyll mutations were found in rice after treatment of the seeds with the chemical. Chromosome aberrations have also been detected in maize treated with ethylene oxide (G28).

Human mutagenic episode for ethylene oxide has been reported in an EPA document (35) as follows:

> "Ehrenbert (36) studied the lymphocytic effects on seven workers who were transiently exposed to a high concentration of EtO for 2 hours after an industrial accident involving an EtO spill. Since two of the seven workers were hospitalized with lung damage, Ehrenbert (37) estimated the level of exposure to be equivalent to 2 hours of continuous exposure to 1500 ppm. Eighteen months afterwards, peripheral blood lymphocytes were examined for chromosomal aberrations, including chromosomal translocations, gaps, breaks, and aneuploidy. When compared with 10 control subjects with ho history of EtO exposure, the incidence of these aberrations was elevated (p 0.05)."

2.7 Teratogenicity and Reproductive Effects

No information was found in searched literature for the teratogenicity of ethylene oxide.

Hollingsworth *et al*. (3) observed atrophic effects on the testes in eight male guinea pigs which were exposed by inhalation to 357 ppm EtO in 123 seven-hour doses during the 176-day study. All animals survived but appreciable degeneration of the testicular tubules and replacement fibrosis was noted. In another test 20 male rats were exposed to 204 ppm EtO for 122 to 157 seven-hour periods during 176 to 226 days were noted to have small testes and slight degeneration of tubules. In view of these findings, the working group on ethylene oxide (35) concluded that "studies conducted with guinea pigs and rats indicate that ethylene oxide can adversely affect the male reproductive organs."

2.8 Metabolic Information

No information found in searched literature.

2.9 Ecological Effects

The rate of pollen collection in bees (Apis mellifera) exposed to fumigated pollen was reduced (G14). Aquatic toxicity rating: TLm 96:100-10 ppm (G16).

2.10 Current Testing

A study is presently underway at Carnegie Mellon University under D.L. Geary and W.M. Snellings to investigate the possible health hazards of long-term inhalation of ethylene oxide vapor.

Groups of rats are inhaling unspecified ethylene oxide concentrations 6 hours a day, 5 days a week for 2 years. Hematologic and blood clinical chemistry evaluations, urinalysis, clotting times, ophthalmologic exams, cytogenic analysis, gross necropsy and histopathological examinations will be performed at each sacrifice interval. The animals will also be palpated for tissue masses periodically.

Mutagenesis, teratogenesis and reproductive effects will also be evaluated (34).

Ethylene oxide (NCI #C50088) has been tentatively selected for carcinogenesis bioassay testings (date approved July 1966) (G12) in rats and mice by inhalation.

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PROPYLENE OXIDE
(Propane, 1,2-Epoxy-)

2.1 Bioaccumulation

There is no potential for bioaccumulation of propylene oxide due to its high solubility (40.5% at 20°C, 59% at 25°C) (G9) and negative log P_{oct} value (log $P_{oct} = -0.13$) (1).

2.2 Contaminants and Environmental Degradation or Conversion Products

IARC monograph (G9) reports propylene oxide specifications from a producer as follows: acetic acid 0.005%, water 0.01%, propionaldehyde 0.05%. Propylene oxide reacts with active hydrogen compounds (e.g., alcohols, amines) and with inorganic chloride in foods to form 1-chloro-2-propanol (G9).

2.3 Acute Toxicity

The NIOSH Registry of Toxic Effects of Chemical Substances (G16) reports the acute toxicity of propylene oxide as follows:

Parameter	Dosage	Animal	Route
LD50	930 mg/kg	rat	oral
LCLo	4000 ppm/4H	rat	inhalation
LC50	1740 ppm/4H	mouse	inhalation
LCLo	2005 ppm/4H	dog	inhalation
LD50	1500 mg/kg	rabbit	skin
LD50	690 mg/kg	guinea pig	oral

Rowe et al. (2) have reviewed the toxicity of propylene oxide. Major toxicity effects and sources cited in this article are as follows:

In a skin contact study, cotton pads moistened with undiluted or diluted (10% and 20% aqueous solutions) propylene oxide were applied to rabbits' skin from 1 to 60 minutes and observed for six to seven days following exposure. Hypermia and edema resulted from all preparations when the duration of skin contact was six minutes or longer. The severe exposures resulted in scar formation.

There is a hazard from inhalation of propylene oxide vapors in experimental animals as shown in Tables 1 and 2 below.

Table 1

Mortality of Female Rats Exposed to Various Concentrations of Propylene Oxide Vapor for Single Periods

Vapor Concentrations		Period of Exposure, Hr.	Rats	
PPM	Mg/L.		Total No.	No. that died
16,000	38.0	0.50	10	10
		0.25	15	0
8,000	19.0	2.0	10	10
		1.0	10	5
		0.50	10	2
		0.25	10	0
4,000	9.5	7.0	10	10
		4.0	10	4
		2.0	10	4
		1.0	5	0
2,000	4.7	7.0	10	0

Table 2

Mortality of Female Guinea Pigs Exposed to Various Concentrations of Propylene Oxide Vapor for Single Periods

Vapor Concentrations		Period of Exposure, Hr.	Guinea Pigs	
PPM	Mg/L.		Total No.	No. that died
16,000	38.0	1.0	5	5
		0.5	5	0
8,000	19.0	4.0	10	10
		2.0	5	1
		1.0	10	0
4,000	9.5	7.0	5	2
		4.0	5	1
		2.0	5	0
2,000	4.7	7.0	5	0

During the exposures the rats and guinea pigs exhibited eye irritation, nasal irritation, difficulty in breathing, drowsiness, weakness and occasionally some incoordination. The amount and extent of the observed symptoms were dependent on the concentration and the duration of exposure (2).

Dogs given single four hour exposures of different concentrations of propylene oxide showed lacrimation, salivation and nasal discharge, vomiting and death. When poisoning progressed far enough to produce vomiting, the dog usually died. The mortality rate in dogs at various concentrations is reported as follows (3) in Table No. 3:

Table 3

Concentration		Mortality	% Mortality after 14 days
PPM	Mg/m^3		
2,481	5,880	3/3 1st hr	100
2,030	4,810	1/3 1st hr, 2/3 1st day	67
2,005	4,750	1/3 1st hr	33
1,363	3,230	0/3 14th day	0

Postmortem examination of dogs reveals that those exposed to concentrations of 2030 and 2480 had marked congestion of the tracheal mucosa and comparable vascular phenomena in the lungs. Spotty alveolar edema and marked prevascular and peribronchial edema were present. Focal areas of subepithelial edema in the terminal bronchioles and necrobiosis of the bronchiolar epithelium were noted. Subpleural hemorrhage was occasionally found. Subendo cardial ecchymoses were noted and are believed to be a secondary effect of the terminal anoxia (3).

2.4 Other Toxic Effects

Guinea pigs, monkeys, rabbits and rats were exposed for 7 hours to propylene oxide vapor, 5 days/week for 6 or 7 months. Rabbits and monkeys, but not guinea pigs or rats tolerated 1095 mg/m^3 (460 ppm). Monkeys, rabbits, rats and male guinea pigs tolerated 464 mg/m^3 (195 ppm). In female guinea pigs increases in the average weight of the lungs were observed. All four species tolerated 243 mg/m^3 (102 ppm) without adverse effect (2,G9). Propylene oxide is about one-third as toxic as ethylene oxide when administered by ingestion or by inhalation, in of the species studied (3,G9).

A paper by McLaughlin (4) has been cited in an IARC monograph (G9) reporting three cases of corneal burns in man from propylene oxide vapor.

The TLV assigned by ACGIH is 100 ppm (approximately 240 mg/m^3) for propylene oxide (G11).

2.5 Carcinogenicity

Only one study (5) of the carcinogenic potential of propylene oxide was found in a secondary source (G9). This study was reviewed by the 1976 IARC expert committee. Propylene oxide was carcinogenic in a limited study in rats by subcutaneous injection and produced local sarcoma (G9). Experimental details outlined in the IARC monograph are as follows:

> "Of 12 rats (age at start not specified) given total doses of 1500 mg/kg bw propylene oxide in arachis oil by s.c. injection within 325 days (dosing schedule not specified), 8 developed local sarcomas after 507-739 days. In a similar experiment in which total doses of 1500 mg/kg bw propylene oxide in water were injected subcutaneously, 1/12 rats developed a local sarcoma after 158 days, and 2 developed local sarcomas after 737 days. In a concurrent experiment, ethylene oxide produced negative results."

2.6 Mutagenicity

Mutagenicity data of propylene oxide has been recently evaluated and reported in one EPA report (G28) as follows:

Propylene oxide has been demonstrated to induce reversions to adenine prototrophy in Neurospora crassa W. 40 "distinctus" A (from strain 38701). At the optimal concentration and time (0.5 M in a suspension containing approximately 132 x 10^6 conidia for one hour), the mutation frequency observed was $80/10^6$ surviving conidia. In untreated controls after one hour of incubation, the mutation frequency was $0/10^6$ survivors. Although a dose-survival relationship was established for propylene oxide during the optimization of the test concentration, there was no data reported indicating that a dose-response effect in induction of mutants had been observed (6). This test was classified "negative/inadequate" as this is the result of a single test in which the chemical was assayed at a dose chosen for optimal survival and mutagenicity.

Propylene oxide was reported to be active in inducing sex-linked recessive lethal mutations (Muller-5 Test) in D. melanogaster Oregon-K. Drosophila sperm were treated by a post-copulatory douche with the chemical. The mutation rate was 1.2% (13 lethals from 12 males/1074 tested) versus 0.06% (1 lethal/1650 tests) in untreated controls. Although the result suggests a positive effect, this report is essentially an abstract, and the data presented are insufficient for evaluation of this test (e.g., no demonstration of dose-response and inadequate description of the experimental method) (7).

Propylene oxide (330 mM) was reported to be inactive in inducing host-range mutations in bacteriophage $T2h^+$. Mutants were identified as phage able to infect $T2h^+$-resistant Escherichia coli B/2 (8).

In addition to Schalet's publication (7) the IARC monograph has cited two Russian articles (9,10) which indicate that propylene oxide induced recessive lethal mutations in Drosophila melanogaster. No experimental details have been reported in the monograph.

Propylene oxide reacts with DNA at neutral pH to yield two principal products, N-7-(2-hydroxypropyl)guanine and N-3-(2-hydroxypropyl)adenine, according to a paper (11) cited in the IARC monograph (G9).

2.7 Teratogenicity

No information found in searched literature.

2.8 Metabolic Information

No information found in searched literature.

2.9 Ecological Effects

Aquatic toxicity rating - TLm 96 over 1000 ppm (G16). Various plastic and cellulose products used as food wrappings and containers when fumigated contained as much as 1500 mg/kg of propylene oxide (12, as reported in G9), which may be of concern for ecological effects when discarded.

2.10 Current Testing

Propylene oxide is currently under test by NCI in rats and mice by the inhalation route. The NCI chemical number is C50099 (G12).

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STATUS OF CARCINOGENICITY STUDIES ON EPOXIDES AT NATIONAL CANCER INSTITUTE*

PART III

Based on their level of exposure, potential carcinogenicity and representative substructures, the following chemicals are on test or were previously considered by the Chemical Selection Working Group (CSWG) for carcinogenesis bioassay testings:

CAS No.	Name	Status
75218	Ethylene oxide	CBDS No. C50088
75569	Propylene oxide	CBDS No. C50099
106898	Epichlorohydrin	CBDS No. C07001
8013078	Epoxidized soy oils	Already considered by CSWG as part of printing ink class; CSWG considered previous tests adequate.
72208	Endrin	Considered as part of organohalide study.
96093	Styrene oxide	Received final NCI approval; will be tested at FCRC

The following four epoxides are representative structures which have also been selected by CSWG for the reasons shown:

Name of Compound	Reason for Nomination
1,2-Epoxybutane	It is the only remaining epoxide having an annual production of greater than 10^8 grams that is not covered by current NCI tests or previous CSWG action. It is representative of simple short chain epoxides and it is mutagenic but has been reported inactive as a carcinogen.
Glycidol	It is a representative short chain epoxide with potential for significant human exposure. Glycidol is mutagenic but has been reported as inactive in carcinogenicity tests where the related compound glycidaldehyde has been reported active.
1,2-Epoxyhexadecane	This epoxide was chosen as a representative long-chain, terminal monoepoxide having potential for significant exposure. Preliminary studies with

Name of Compound	Reason for Nomination
1,2-Epoxyhexadecane (Continued)	mice indicate it may be carcinogenic.
3,4-Epoxycyclohexylmethyl-3,4-epoxycyclohexane carcoxylate	This was recommended as the only diepoxide with potential for significant exposure that has not yet been adequately tested; it is closely related to 3,4-epoxy-6-methylcyclohexylmethyl-3,4-epoxy-6-methylcyclohexane carboxylate which is carcinogenic to mouse skin.

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[*] "Epoxides Class Study" conducted by a class working group of the Chemical Selection Working Group.

INFORMATION ON STRUCTURAL ANALOGS (1)

PART IV

A number of alkyl epoxides have been tested for carcinogenicity mostly by painting the skin of mice and observing the formation of papillomas and carcinomas. Although many of these chemicals are not of major industrial importance and some may only represent laboratory curiosities, it is important to realize that not all of these alkyl epoxides are carcinogenic; but it is not clear at this time what factors in chemical structure limit such carcinogenicity.

Regarding the carcinogenic potency of diepoxides, it can be stated that nearly all diepoxides are far more carcinogenic than monoepoxides and the reason is to be found in the capability of diepoxides to cause cross-linking between chains of DNA. Although diepoxides have been suggested at one time as chemotherapeutic agents for the treatment of cancer, it is unlikely that these compounds will become of major industrial significance.

Because of the far lower toxicity of monoepoxides, it seems of importance to put the available literature on the carcinogenicity of these compounds that have not been dealt with earlier in the dossier together in table form (See Table 1).

Epoxides with additional functional groups have not been considered as structural analogs in this discussion, but a great number of such analogs like epichlorohydrin, glycidal, and epoxystearic acid have been found carcinogenic. These compounds will have to be considered as a separate group of epoxides and a separate dossier will have to be prepared.

TABLE 1. CARCINOGENICITY OF ALKYL EPOXIDES (2, 3, 4)

Compound	Concentration in acetone	Tumors	
		Papillomas	Carcinomas
Hexaepoxysqualene	1%	1	0
1,2,3,4-Diepoxybutane	3%	10	6
1,2,4,5-Diepoxypentane	10%	10	3
1,2,5,6-Diepoxyhexane	5%	4	0
1,2,6,7-Diepoxyheptane	1%	9	1
1,2,7,8-Diepoxyoctane	1%	7	4
1-ethyleneoxy-3,4-epoxycyclohexane	10% (Benzene)	5	4
1,2,3,4-Diepoxycyclohexane	10%	0	0
1,2,5,6-Diepoxycyclooctane	10%	0	0
1-ethyl-3,4-epoxycyclohexane	10%	0	0
Ethyleneoxycyclohexane	10%	0	0
Epoxycyclohexane	10% (Benzene)	0	0
Epoxycyclooctane	10%	0	0
1,2-Epoxybutene-3	no solvent	2	1
1,2-Epoxybutane.	10%	0	0
1,2-Epxoydodecane	2%	0	0
1,2-Epoxyhexadecane	10%	2	1

30 male Swiss Millerton mice were painted 3x weekly with 100 mg solution/paint for life.

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ALKYL PHTHALATES

TABLE OF CONTENTS

Page

Overview II-1

Alkyl phthalates, long chain

Part I - General Information

Bis(2-Ethylhexyl) phthalate II-3

Dicyclohexyl phthalate II-6

Diisodecyl phthalate II-8

Diisooctyl phthalate II-10

Dioctyl pthalate II-12

Ditridecyl phthalate II-14

n-Octyl n-decyl phthalate II-16

Summary of characteristics II-18

Alkyl phthalates, short chain

Part I - General Information

Dibutyl phthalate II-19

Diethyl phthalate II-22

Dimethyl phthalate II-24

Summary of characteristics II-26

Specific References II-27

Part II - Biological Properties

2.1 Bioaccumulation II-28

2.2 Contaminants and Environmental Degradation or Conversion Products II-29

2.3 Acute Toxicity II-31

2.4 Other Toxic Effects II-31

Page

Part II - Biological Properties (Continued)

2.5 Carcinogenicity II-31
2.6 Mutagenicity II-37
2.7 Teratogenicity II-38
2.8 Metabolic Information II-41
2.9 Ecological Effects II-44
2.10 Current Testing II-50
References II-51

ALKYL PHTHALATES

AN OVERVIEW

This category consists of alkyl esters of 1,2-benzene dicarboxylic acid. They are generally water-insoluble liquids.

Many of the alkyl phthalates are produced in large volumes; annual production of both (di(2-ethylhexyl)phthalate) and diisodecyl phthalate) exceed one hundred million pounds.

Alkyl phthalates are primarily used as plasticizers for resins, including vinyl chloride resins. They also have numerous household applications, such as in model cements, paints and wood finishes.

The di(2-ethylhexyl) phthalate has been estimated to be released into the environment at a rate of 440 million pounds annually, while about 30 million pounds of dibutyl phthalate and 20 million pounds of diethyl phthalate are released. It is estimated that over 3 million U.S. workers are occupationally exposed to alkyl phthalates.

Alkyl phthalates are relatively stable, breaking down only slowly to monophthalates or phthalic acid. High bioaccumulation factors for alkyl phthalates have been observed in aquatic invertebrates and plants. Fish show much lower bioaccumulation of phthalates, apparently because of superior abilities to metabolize and excrete phthalates. Widespread occurrence of the phthalate esters in aquatic ecosystems has been reported.

Although the alkyl phthalates are relatively toxic to fish and aquatic invertebrates, they have a low order of acute toxicity to mammals and birds. The shorter chain esters are more toxic to mammals than the longer chain compounds. The mutagenicity and carcinogenicity of these chemicals are not adequately established. However, positive teratogenic results have been reported.

The chronic toxicity has been indicated in sub-lethal exposures that inhibited reproduction in daphnia, reduced the survival of eggs and fry of fish and reduced egg shell thickness in birds. Biological significance levels and the levels and frequency of occurrence of residues in fish have not been adequately determined.

ALKYL PHTHALATES - LONG CHAIN

PART I

GENERAL INFORMATION

I. Bis(2-Ethylhexyl) phthalate

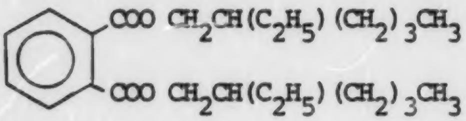
1.1 Identification CAS No.: 000117817
NIOSH No.: TI03500

1.2 Synonyms and Trade Names

1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester; phthalic acid, bis (2-ethylhexyl) ester; Compound 889; DEHP; di(2-ethylhexyl) orthophthalate; di(2-ethylhexyl) phthalate; di-sec-octyl phthalate; DOP; 2-ethylhexyl phthalate; Flexol DOP; Flexol plasticizer DOP; Hercoflex 260; Octoil; Pittsburgh PX-138; RC plasticizer DOP; Witcizer 312; Truflex DOP; Staflex DOP

(G16,G23)

1.3 Chemical Formula and Molecular Weight



$C_{24}H_{38}O_4$ Mol. Wt. 390.54

(G23)

1.4 Chemical and Physical Properties

1.4.1 Description: Light-colored odorless liquid; combustible (G21)

1.4.2 Boiling Point: 231° C at 5mm (G25)

1.4.3 Melting Point: -46° C (G25)

1.4.4 Absorption Spectrometry:

No information found in sources searched

1.4.5 Vapor Pressure:

No information found in sources searched

1.4.6 Solubility: Insoluble in water;
Soluble in all proportions in mineral oil (G21)

1.4.7 Octanol/Water Partition Coefficient:

$\log P_{oct} = 3 - 4$ (estimate) (G36)

1.5 Production and Use

1.5.1 Production:

435	Million lbs	(1972)	(G28)
302.492	Million lbs	(1975)	(G24)
296.739	Million lbs	(1976)	(G24)

1.5.2 Use: As a commercial plasticizer in vinyl chloride resins; in vacuum pumps; as a plasticizer in polystyrene; as a plasticizer for many resins and elastomers; in automotive seating, interior trim, and Landau roofs

(G21, G23, G25, G32)

Consumer Product Information:

Category	no. of bis(2-ethylhexyl) phthalate containing products	No. of bis(2-ethylhexyl) phthalate products in category / total no. of products in category x100
paints, varnishes, shellac, rust preventatives, etc.	49	0.4%
flame retardant chemicals	11	1.9%
household aerosols	67	1.8%
chemical deodorizers	2	0.6%
adhesives and adhesive products, incl. glue	3	0.6%

(G27)

The 132 chemicals surveyed contained an average of 3.5% bis(ethylhexyl) phthalate

Bis (2-ethylhexyl) phthalate is present in:

aerosol paints
lacquers
woodfinishes
model cement
household cement
children's "Plastigoop" (G35)

1.6 Esposure Estimates

1.6.1 Release Rate: 441.6 Million lbs (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 333

Estimated no. of persons exposed: 693,000*

*rough estimate (G29)

1.7 Manufacturers

- BASF Wyandotte Corp.
- B.F. Goodrich Co.
- Continental Oil Co.
- Tennessee Eastman Co.
- Exxon Chemical Co.
- W.R. Grace & Co.
- Tenneco Chemicals, Inc.
- Monsanto Co.
- Reichhold Chemicals, Inc.
- Teknor Apex Co.
- Union Carbide Corp.
- USS Chemicals Div. of U.S. Steel Corp.

(G24)

II. Dicyclohexyl phthalate

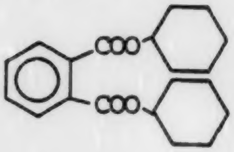
1.1 Identification

CAS No.: 000084617
NIOSH No.:

1.2 Synonyms and Trade Names

Phthalic acid, dicyclohexyl ester; DCHP (G21,G22)

1.3 Chemical Formula and Molecular Weight



$C_{20}H_{26}O_4$ Mol. Wt. 330.43

(G21,G22)

1.4 Chemical and Physical Properties

1.4.1 **Description:** Prisms (from alcohol); white granular solid; nonvolatile; mildly aromatic odor; combustible

(G21,G22)

1.4.2 **Boiling Point:**

No information found in sources searched

1.4.3 **Melting Point:** 66° C (G22)

1.4.4 **Absorption Spectrometry:**

No information found in sources searched

1.4.5 **Vapor Pressure:**

No information found in sources searched

1.4.6 **Solubility:** Insoluble in water;
Soluble in alcohol, ether, and most organic solvents

(G21,G22)

1.4.7 **Octanol/Water Partition Coefficient:**

$\log P_{oct} = 3 - 4$ (estimate) (G36)

1.5 Production and Use

1.5.1 Production:

No information found in sources searched

1.5.2 Use: As a plasticizer for nitrocellulose, ethyl cellulose, chlorinated rubber, polyvinyl acetate, polyvinyl chloride, and other polymers; in specialty plastics; in adhesives

(G21,G25)

1.6 Esposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure:

Rank: 1963

Estimated no. of persons exposed: 25,000*

*rough estimate (G29)

1.7 Manufacturers

Monsanto Co.
Pfizer, Inc. (G24)

ALKYL PHTHALATES - LONG CHAIN

III. Diisodecyl phthalate

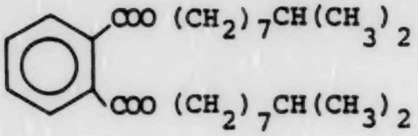
1.1 Identification

CAS No.: 026761400
NIOSH No.:

1.2 Synonyms and Trade Names

DIDP (G21)

1.3 Chemical Formula and Molecular Weight



$C_{28}H_{46}O_4$ Mol. Wt. 446

(G21,G25)

1.4 Chemical and Physical Properties

1.4.1 **Description:** Clear liquid with a mild odor (G21)

1.4.2 **Boiling Point:** 250 - 257° C at 4 mm (G21)

1.4.3 **Melting Point:**

No information found in sources searched

1.4.4 **Absorption Spectrometry:**

No information found in sources searched

1.4.5 **Vapor Pressure:**

No information found in sources searched

1.4.6 **Solubility:** Insoluble in glycerol, glycols, and some amines; Soluble in most other organics and oils (G21,G25)

1.4.7 **Octanol/Water Partition Coefficient:**

$\log P_{oct} = 3 - 4$ (estimate) (G36)

1.5 Production and Use

1.5.1 Production:

125	Million lbs	(1970)	(G25)
105.668	Million lbs	(1975)	(G24)
143.129	Million lbs	(1976)	(G24)

1.5.2 Use:

As a commercial plasticizer in vinyl chloride resins; in calendered film and sheeting; in coated fabrics; in wire and cable extrusion

(G21,G32)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure:

Rank: 1136

Estimated no. of persons exposed: 100,000*

*rough estimate (G29)

1.7 Manufacturers

BASF Wyandotte Corp.
Continental Oil Co.
Tennessee Eastman Co.
Exxon Chemical Co.,
W. R. Grace & Co.
Tenneco Chemicals, Inc.
Monsanto Co.
Reichhold Chemicals, Inc.
Hooker Chemical Corp.
Teknor Apex Co.
USS Chemicals Div. of U.S. Steel Corp. (G24)

ALKYL PHTHALATES - LONG CHAIN

IV. Diisooctyl Phthalate

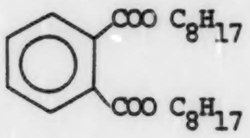
1.1 Identification

CAS No.:
NIOSH No.:

1.2 Synonyms and Trade Names

DIOP (G21)

1.3 Chemical Formula and Molecular Weight



$C_{24}H_{38}O_4$ Mol. Wt. 390.54

(G21)

1.4 Chemical and Physical Properties

1.4.1 **Description:** Isomeric esters obtained from phthalic anhydride and the mixed octyl alcohols; nearly colorless viscous liquid; mild odor; combustible

(G21)

1.4.2 **Boiling Point:** 370° C (G21)

1.4.3 **Melting Point:** $< -50°$ C (G25)

1.4.4 **Absorption Spectrometry:**

No information found in sources searched

1.4.5 **Vapor Pressure:**

No information found in sources searched

1.4.6 **Solubility:** Insoluble in water;
Soluble in oils

(G21,G25)

1.4.7 **Octanol/Water Partition Coefficient:**

$\log P_{oct} = 3 - 4$ (estimate) (G36)

1.5 Production and Use

1.5.1 Production: 32.3 Million lbs (1972) (G28)

1.5.2 Use: As a commercial plasticizer in vinyl chloride resins; as a plasticizer for cellulosic and acrylate resins and synthetic rubber (G21)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure:

Rank: 2703

Estimated no. of persons exposed: 10,000*

*rough estimate (G29)

1.7 Manufacturers

Reichhold Chemicals, Inc.
USS Chemicals Div. of U.S. Steel Corp. (G24)

V. Dioctyl phthalate

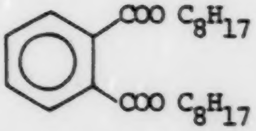
1.1 Identification CAS No.: 000117840
NIOSH No.: TI19250

1.2 Synonyms and Trade Names

Phthalic acid, dioctyl ester; *o*-benzenedicarboxylic acid, dioctyl ester; Celluflex COP; dioctyl *o*-benzenedicarboxylate; *n*-dioctyl phthalate; octyl phthalate; Polycizer 162; PX-138

(G16)

1.3 Chemical Formula and Molecular Weight



$C_{24}H_{38}O_4$ Mol. Wt. 390.54

(G25)

1.4 Chemical and Physical Properties

1.4.1 Description: Colorless, odorless, stable, oily liquid (G25)

1.4.2 Boiling Point: 248° C (G25)

1.4.3 Melting Point: -25° C (G25)

1.4.4 Absorption Spectrometry:

No information found in sources searched

1.4.5 Vapor Pressure:

No information found in sources searched

1.4.6 Solubility: Insoluble in water;
Soluble in all proportions in mineral oil

(G25)

1.4.7 Octanol/Water Partition Coefficient:

$\log P_{oct} = 3 - 4$ (estimate) (G36)

1.5 Production and Use

1.5.1 Production:

No information found in sources searched

1.5.2 Use: As a commercial plasticizer in vinyl chloride resins

(G32,G35)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure:

No information found in sources searched

1.7 Manufacturer

Eastman Kodak Co. (G24)

ALKYL PHTHALATES - LONG CHAIN

VI. Ditridecyl phthalate

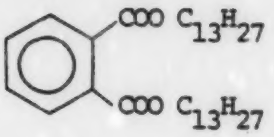
1.1 Identification

CAS No.: 000119062
NIOSH No.:

1.2 Synonyms and Trade Names

DTDP (G21)

1.3 Chemical Formula and Molecular Weight



$C_{34}H_{58}O_4$ Mol. Wt. 530.83

(G21)

1.4 Chemical and Physical Properties

1.4.1 Description: Colorless liquid; combustible (G21)

1.4.2 Boiling Point: > 285° C at 5 mm (G21)

1.4.3 Melting Point:

No information found in sources searched

1.4.4 Absorption Spectrometry:

No information found in sources searched

1.4.5 Vapor Pressure:

No information found in sources searched

1.4.6 Solubility:

No information found in sources searched

1.4.7 Octanol/Water Partition Coefficient:

$\log P_{oct} = 3 - 4$ (estimate) (G36)

1.5 Production and Use

1.5.1 Production:

23.9	Million lbs	(1972)	(G28)
15.664	Million lbs	(1975)	(G24)
10.472	Million lbs	(1976)	(G24)

1.5.2 Use: As a plasticizer (G21)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure:

Rank: 2710

Estimated no. of persons exposed: 10,000*

*rough estimate (G29)

1.7 Manufacturers

Exxon Chemical Co.
W. R. Grace & Co.
Tenneco Chemicals, Inc.
Reichhold Chemicals, Inc.
Hooker Chemical Corp.
Teknor Apex Co.
USS Chemicals Div. of U.S. Steel Corp. (G24)

ALKYL PHTHALATES - LONG CHAIN

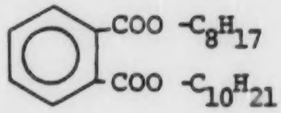
VII. n-Octyl n-decyl phthalate

1.1 Identification CAS No.: 000119073
NIOSH No.:

1.2 Synonyms and Trade Names

No information found in sources searched

1.3 Chemical Formula and Molecular Weight



$C_{26}H_{42}O_4$ Mol. Wt. 418.62

1.4 Chemical and Physical Properties

1.4.1 Description: Clear liquid; mild characteristic odor; combustible (G21)

1.4.2 Boiling Point: 232 - 267° C at 4 mm (G21)

1.4.3 Melting Point:

No information found in sources searched

1.4.4 Absorption Spectrometry:

No information found in sources searched

1.4.5 Vapor Pressure:

No information found in sources searched

1.4.6 Solubility:

No information found in sources searched

1.4.7 Octanol/Water Partition Coefficient:

$\log P_{oct} = 3 - 4$ (estimate) (G36)

1.5 Production and Use

1.5.1 Production:

No information found in sources searched

1.5.2 Use:

As a commercial plasticizer in vinyl chloride resins (G21

1.6 Exposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure:

Rank: 1999

Estimated no. of persons exposed: 24,000*

*rough estimate (G29)

1.7 Manufacturers

Reichhold Chemicals, Inc.
Teknor Apex Co.
USS Chemicals Div. of U.S. Steel Corp. (G24)

ALKYL PHTHALATES, LONG CHAIN

SUMMARY OF CHARACTERISTICS

Name	Solubility	Log P_{oct}	Estimated Environmental Release (Million lbs)	Production (Million lbs)	Estimated no. of persons exposed (Occupational)	Use
Bis(2-ethylhexyl) phthalate	i in H_2O; ∞ in mineral oil	3-4 (estimate)	441.6	~435 (1972) 302.492 (1975) 296.739 (1976)	~693,000	Plasticizer for many resins and elastomers; vacuum pumps; automotive seating
Dicyclohexyl phthalate	i in H_2O; s in alc, eth, and most os	3-4 (estimate)	*	* *	~25,000	Plasticizer for many polymers; specialty plastics; adhesive
Diisodecyl phthalate	i in glycerol, glycols, some amines; s in most os and oils	3-4 (estimate)	*	~125 (1970) 105.668 (1975) 143.129 (1976)	~100,000	Plasticizer in vinyl chloride resins; coated fabrics; cable and film
Disooctyl phthalate	i in H_2O; s in oils	3-4 (estimate)	*	32.3 (1972)	~10,000	Plasticizer in many resins and synthetic rubber
Dioctyl phthalate	i in H_2O; ∞ in mineral oil	3-4 (estimate)	*	* *	*	Plasticizer in vinyl chloride resins
Ditridecyl phthalate	*	3-4 (estimate)	*	23.9 (1972) 15.664 (1975) 10.472 (1976)	~10,000	Plasticizer
n-Octyl n-decyl phthalate	*	3-4 (estimate)	*	* *	~24,000	Plasticizer in vinyl chloride resins

* No information found in sources searched.

ALKYL PHTHALATES - SHORT CHAIN

PART I

GENERAL INFORMATION

I. Dibutyl phthalate

1.1 Identification

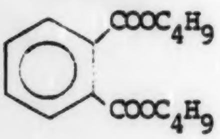
CAS No.: 000084742
NIOSH No.: TI08750

1.2 Synonyms and Trade Names

Benzene-*o*-dicarboxylic acid, di-*n*-butyl ester; di-*n*-butyl phthalate; *o*-benzenedicarboxylic acid, dibutyl ester; phthalic acid, dibutyl ester; DBP; Celluflex DBP; Elaol; Hexaplas M/B; Palatinol C; Polycizer DBP; PX 104; Staflex DBP; Witicizer 300

(G16,G23)

1.3 Chemical Formula and Molecular Weight



$C_{16}H_{22}O_4$ Mol. Wt. 278.35

(G22)

1.4 Chemical and Physical Properties

1.4.1 **Description:** Colorless, odorless, stable, oily liquid; combustible; nonvolatile (G21,G25)

1.4.2 **Boiling Point:** 340° C (G22)

1.4.3 **Melting Point:**

No information found in sources searched

1.4.4 **Absorption Spectrometry:**

$\lambda_{max}^{alcohol} = 226, 272$ nm

$\log \epsilon = 3.98, 3.18$ (G22)

1.4.5 **Vapor Pressure:** 1 mm at 148.2° C (G22)

1.4.6 **Solubility:** Soluble in water (0.45g/100 ml at 25°C)
Soluble in all proportions in alcohol, ether and benzene
(G22,G19 in 1)

1.4.7 **Octanol/Water Partition Coefficient**

$\log P_{oct} = 2.2$ (estimate) (G36)

1.5 Production and Use

1.5.1 **Production:**			
29.1	Million lbs	(1972)	(G28)
12.264	Million lbs	(1975)	(G24)
13.702	Million lbs	(1976)	(G24)

1.5.2 **Use:** As a plasticizer in nitrocellulose lacquers, elastomers; in explosives, nail polish and solid rocket propellants; as a solvent for perfume oils; as a perfume fixative; as a textile lubricating agent; in safety glass; in insecticides and chigger repellent; in printing inks; as a resin solvent; in paper coatings; in adhesives

(G21)

Consumer Product Information:

Category	No. of dibutyl phthalate containing products	No. of dibutyl phthalate products in category / total no. of products in category x100
cleaning agents and compounds	4	0.2%
paints, varnishes, shellac, rust preventatives, etc.	67	0.6%
flame retardant chemicals	12	2.0%
household aerosols	5	0.1%
adhesives and adhesive products, incl. glue	14	2.6%
caulking and spackle	5	7.7%
floor waxes	1	0.5%

The 108 products surveyed contained an average of 1.9% dibutyl phthalate

(G27)

Dibutyl phthalate is present in:

aerosol antiperspirants and deodorants
nail enamels, base coats and top coats
tractor and implement finishes
rubber sealants
floor waxes
emergency light markers (G35)

1.6 Exposure Estimates

1.6.1 **Release Rate:** 29.5 Million lbs (G28)

1.6 Exposure Estimates (Continued)

1.6.2 NOHS Occupational Exposure:

Rank: 259

Estimated no. of persons exposed: 1,006,000*

*rough estimate (G29)

1.7 Manufacturers

Sherwin Williams
Argus Chemical Corp.
BASF Wyandotte Corp.
Cincinnati Milacron Inc.
Continental Oil Co.
Diamond Shamrock Corp.
Exxon Corp.
Filo Color and Chemical Corp.
FMC Corp.
B. F. Goodrich Co.
W. R. Grace & Co.
Hooker Chemical Corp.
Kay-Fries Chemical, Inc.
Monsanto Co.
Pfizer, Inc.
Reichhold Chemicals
Rohm and Haas Co.
Teknor Apex Co.
Tenneco Chemicals, Inc.
Tennessee Eastman Co.
Union Camp Corp.
United States Steel Corp.
Commerical Solvents Corp.
Union Carbide Corp.

(G25,G24,G31)

ALKYL PHTHALATES - SHORT CHAIN

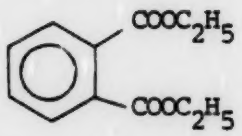
II. Diethyl phthalate

1.1 **Identification** CAS No.: 000084662
NIOSH No.: TI10500

1.2 **Synonyms and Trade Names**

1,2-Benzenedicarboxylic acid, diethyl ester; ethyl phthalate; Anozol; Neantine; Palatinol A; Phthalol; Placidol E; Solvanol; DEP; phthalic acid, diethyl ester
(G21,G16)

1.3 **Chemical Formula and Molecular Weight**



$C_{12}H_{14}O_4$ Mol. Wt. 222.24
(G22)

1.4 **Chemical and Physical Properties**

1.4.1 **Description:** Colorless to water white, practically odorless, oily liquid; bitter, disagreeable taste; combustible
(G23,G21)

1.4.2 **Boiling Point:** 295° C (G23)

1.4.3 **Melting Point:** No information found in sources searched

1.4.4 **Absorption Spectrometry:**

$$\lambda_{max}^{alcohol} = 225,\ 275\ nm;$$

$$\log \epsilon = 3.9,\ 3.1$$
(G22)

1.4.5 **Vapor Pressure:** 1 mm at 108.8° C (G22)

1.4.6 **Solubility:** Insoluble in water;
Soluble in acetone and benzene;
Soluble in all proportions in alcohol;
ether and many other organic solvents
(G22,G23)

1.4.7 **Octanol/Water Partition Coefficient**

$\log P_{oct} = 1.8$ (estimate) (G36)

1.5 Production and Use

1.5.1 **Production:**

19.0	Million lbs	(1972)	(G28)
11.661	Million lbs	(1975)	(G24)
16.135	Million lbs	(1976)	(G24)

1.5.2 **Use:** As a solvent for nitrocellulose, cellulose acetate; as a plasticizer; as a wetting agent; in insecticidal sprays; as a camphor substitute; in plastics; as a perfume fixative and solvent; as an alcohol denaturant; in mosquito repellents; as a plasticizer in solid rocket propellants

(G21)

Consumer Product Information:

Diethyl phthalate is present in:

tarnish preventatives for gold, silver and brass.
colognes, perfumes, bathoils, shampoo

(G35)

1.6 Exposure Estimates

1.6.1 **Release Rate:** 19.3 Million lbs (G28)

1.6.2 **NOHS Occupational Exposure:**

Rank: 171

Estimated no. of persons exposed: 1,240,000

(G29)

1.7 Manufacturers

Kay-Fries Chemicals, Inc.
Monsanto Co.
Pfizer, Inc.
Eastman Kodak Co.: Tennessee Eastman Co. Div.

(G24)

ALKYL PHTHALATES - SHORT CHAIN

III. Dimethyl phthalate

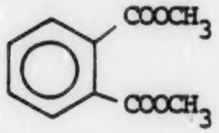
1.1 **Identification** CAS No.: 000131113
NIOSH No.: TI15750

1.2 **Synonyms and Trade Names**

Avolin; 1,2-benzenedicarboxylic acid, dimethyl ester; dimethyl benzene-orthodicarboxylate; DMP; Ent 262; Fermine; methyl phthalate; Mipax; NTM; Palatinol M; phthalic acid, dimethyl ester; phthalic acid, methyl ester; Solvanom; Solvarone

(G16)

1.3 **Chemical Formula and Molecular Weight**



$C_{10}H_{10}O_4$ Mol. Wt. 194.19

(G22)

1.4 **Chemical and Physical Properties**

1.4.1 **Description:** Colorless to pale yellow oily liquid; odorless to slight aromatic odor; combustible (G21,G22,G23)

1.4.2 **Boiling Point:** 283.8° C (G22)

1.4.3 **Melting Point:** 0-2° C (G22)

1.4.4 **Absorption Spectrometry:**

$$\lambda_{max}^{alcohol} = 225, 274 \text{ nm};$$

$$\log \epsilon = 3.92, 3.10$$ (G22)

1.4.5 **Vapor Pressure:** 1 mm at 100.3° C (G22)

1.4.6 **Solubility:** Insoluble in petroleum ether, and other paraffin hydrocarbons;
Soluble in benzene, water (0.5g/100 ml);
Soluble in all proportions in alcohol, ether and chloroform

(G22,G23,G19 in 1)

1.4 Chemical and Physical Properties (Continued)

1.4.7 Octanol/Water Partition Coefficient:

$\log P_{oct} = 1.5$ (estimate) (G36)

1.5 Production and Use

1.5.1 Production:

6.771 Million lbs	(1975)	
8.836 Million lbs	(1976)	(G24)

1.5.2 Use:

As a plasticizer for nitrocellulose and cellulose acetate, resins, rubber and in solid rocket propellants; in lacquers; in plastics; in rubber; in coating agents; in safety glass; in molding powders; in insect repellents; in perfumes (G21)

Consumer Product Information:

Dimethyl phthalate is present in:

plastic fillers (G35)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure

Rank: 1691

Estimated no. of persons exposed: 36,000*

*rough estimate (G29)

1.7 Manufacturers

Kay-Fries Chemicals, Inc.
Monsanto Co.
Pfizer, Inc.
Eastman Kodak Co.: Tennessee Eastman Co. Div.
Tanatex Chemical Corp.

(G24)

ALKYL PHTHALATES, SHORT CHAIN

SUMMARY OF CHARACTERISTICS

Name	Solubility	Log P_{oct}	Estimated Environmental Release (Million lbs)	Production (Million lbs)	Estimated no. of persons exposed (Occupational)	Use
Dibutyl phthalate	ss in H_2O;∞ in alc, eth and bz	2.2 (estimate)	29.5	29.1 (1972) 12.264 (1975) 13.702 (1976)	~1,006,000	Plasticizer; solvent; insecticide; ink; coatings; adhesives
Diethyl phthalate	i in H_2O; s in ace and bz;∞ in alc, eth and many other os	1.8 (estimate)	19.3	19.0 (1972) 11.661 (1975) 16.135 (1976)	1,240,000	Solvent; plasticizer; insecticide; fixative; wetting agent
Dimethyl phthalate	ss in H_2O, i in peth, and other paraffin hydrocarbons; s in bz; in alc, eth, and chl	1.5 (estimate)	*	6.771 (1975) 8.836 (1976)	~36,000	Plasticizer; insect repellent

* No information found in sources searched.

SPECIFIC REFERENCE FOR PART I

1. Autian, J. Toxicity and Health Threats of Phthalate Esters: Review of the Literature Environ. Health Perspec. 4 (1973).

ALKYL PHTHALATES

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

Metcalf et al. (1) carried out studies to determine the uptake of labeled DEHP directly from water by various aquatic plants and animals. They also evaluated the magnification properties of DEHP in a laboratory model ecosystem that included a terrestrial-aquatic interface and a seven-element food chain. The authors concluded that DEHP closely resembles DDT in the rate of uptake and storage, that DEHP partitions strongly in lipids of plants and animals and is concentrated in moving through the food chains. At the end of the 33-day model ecosystem study, Oedogonium (algae) had bioconcentrated DEHP by a factor of 53,890, Physa (snails) by 21,480, Culex (mosquito larvae) by 107,670, and Gambusia (fish) by 130. Failure to bioaccumulate DEHP in Gambusia, indicates that DEHP is metabolized by fish. Similar experiments with guppies show that they metabolize DEHP rapidly while invertebrates and plants degrade DEHP at a much slower rate (1). These results appear to account for high bioaccumulation in invertebrates and plants.

A laboratory study reported the accumulation of DEHP by fathead minnows to levels 160 to 1130 times the concentration in water. 12.3 days after the fish were transferred to fresh water, 50% of the DEHP was eliminated (2).

Bioaccumulation of DNBP by aquatic invertebrates was studied by exposing the organisms to DNBP containing 14C-labeled tracer (3,4). From what appear to be almost identical experiments, the two papers reported different bioaccumulation factors. Sanders, Mayer and Walsh (3) report the 14-day bioaccumulation factors of 5000 and 6700 for waterfleas (*Daphnia magna*) and scud (*Gammarus pseudolimneuis*), respectively. Mayer and Sanders (4) report these figures as 400 and 1400, respectively. However, the data from Sanders *et al*. are from flow-through bioassays and those from Mayer and Sanders are unspecified and may be from static bioassays.

Environmental samples that were analyzed for phthalates substantiated the laboratory predictions of phthalate bioaccumulation. Mayer, Stalling and Johnson (5) reported concentrations of 3.2 ppm DEHP in channel catfish. Tadpoles were found to contain 0.5 ppm DNBP (5). A survey of 145 commercial catfish farms revealed that 95% of the fish analyzed contained DEHP residues. The average DEHP concentration was 3.15 ppm (6). Water concentration levels were not reported.

The log octanol-water partition ratios of the phthalates are in the range expected to cause bioaccumulation. High bioaccumulation factors are indeed observed with aquatic invertebrates and plants (up to 100,000). Bioaccumulation factors are much lower with fish (130-1130) apparently owing to their superior ability to metabolize and excrete the phthalates.

2.2 Contaminants and Environmental Degradation or Conversion Products

In an aquatic model ecosystem di-n-octyl phthalate exhibited a half-life of about five days. Major degradation products in the water were phthalic acid and mono-octyl phthalate (8).

In another study, ^{14}C-DEHP rapidly decreased in the guppy (*Lebistis reticulatus*) from 88.5% of the total radioactivity after one day to 37.1% after two days with concomitant increase of polar metabolites (45, as reported in 1). Products were phthalic acid (23.8%) and small amounts of a metabolite believed to be phthalic anhydride. Degradation of DEHP was much slower with the water flea, snail and the aquatic plant *Elodea*. Products were similar to those from the guppy.

Specific data concerning individual esters follows:

Dibutyl Phthalate

BOD: 19% of theoretical after 5 days at 20°C

Total theoretical oxygen demand = 2.25 (gm/kg)

Reacts with oxidizing agents

(G15)

Di-2-ethylhexyl Phthalate

Impurities in product: 2-ethylhexanol, phthalic acid, mono-ethylhexylphthalate, water, 2-ethylhexylbenzoate. Reacts with oxidizing materials, unreactive towards peroxide and ozone.

Activity towards hydroxyl radical: $t_{1/2}$= 1 day

It hydrolyzes fairly rapidly at pH 10 ($t_{1/2}$ = 8 days) but much more slowly at lower pH values.

(G14.G15)

Diisodecyl phthalate

Reacts with oxidizing materials

(G15)

Diisoctyl Phthalate

Reacts with oxidizing materials

(G15)

n-Octyl-n-decyl Phthalate

Reacts with oxidizing materials

(G15)

2.3 Acute Toxicity

The NIOSH Registry of Toxic Effects of Chemical Substances (G16) reports the acute toxicity of phthalate esters as shown in Table 1.

The alkyl phthalates have a low order of acute toxicity in mammals. The shorter chain esters are more toxic than the longer chain compounds (9).

Some of the acute toxic effects of phthalate esters may be attributable to contamination with phthalic anhydride (10).

2.4 Other Toxic Effects

The effects of repeated doses of alkyl phthalates on humans and various laboratory animals are summarized in Table 2. Data for this table are taken directly from the secondary source cited; the primary reference refers to the article which originally reported the result. Nearly all of the investigations concluded that the phthalates constitute a chemical family of very low order of toxicity, as measured by ingestion methods (11).

2.5 Carcinogenicity

Two reviewers reported no evidence of carcinogenicity for these materials. Krauskopf, in 1973, reviewed the literature on the oral toxicity of the phthalate esters. Though numerous long term feeding studies

TABLE 1

ACUTE DOSAGES OF ALKYL PHTHALATES (G16)

Compound		Dosage	Animal	Route
Dibutyl Phthalate	TDLo (CNS)	140 mg/kg	human	oral
	LD50	3050 mg/kg	rat	intraperitoneal
Diethyl Phthalate	LD50	5058 mg/kg	rat	intraperitoneal
	LD50	2749 mg/kg	mouse	intraperitoneal
	LDLO	1000 mg/kg	rabbit	oral
Dimethyl Phthalate	LD50	3375 mg/kg	rat	intraperitoneal
	LD50	1580 mg/kg	mouse	intraperitoneal
	LCLO	1000 ppm	cat	inhalation
	LD50	4400 mg/kg	rabbit	oral
	LD50	2400 mg/kg	guinea pig	oral
	LD50	8500 mg/kg	chicken	oral
Diethylhexyl Phthalate	TDLO (GIT)	143 mg/kg	man	oral
	LD50	31 gm/kg	rat	oral
	LDLO	300 mg/kg	rat	intravenous
	LD50	14 gm/kg	mouse	intraperitoneal
	LD50	34 gm/kg	rabbit	oral
	LD50	10 gm/kg	guinea pig	skin
Dioctyl Phthalate	TDLO (GIT)	143 mg/kg	man	oral

TOXICITY ORDER

Rat (i.p.)	Dibutyl $>$ dimethyl $>$ diethyl
Mouse (i.p.)	Dimethyl $>$ diethyl $\gg$ diethylhexyl
Rabbit (oral)	Diethyl $>$ Dimethyl $\gg$ Diethylhexyl

TABLE 2

SUMMARY OF CHRONIC TOXIC EFFECTS OF PHTHALATE ESTERS

#	Compound	Species	Dose	Period	Effects	References Primary	 Secondary
1	Dibutyl Phthalate (DBP)	rats	100 mg/kg/day	5 generations (some for 21 months)	No poisonous or carcinogenic effects at all dose levels. Normal weight gains and reproductive patterns.	12	11
			300 mg/kg/day	3 generations (some for 21 months)			
			500 mg/kg/day	3 generations (some for 15 months)			
2	DBP	rats	2-5 mg/kg/day	6 months	No effect; recommended maximum level of 2 mg/l in reservoir due to toxicity; taste and odor threshold at 5 mg/l	13	11
3	DBP	rats	0.01% day	1 year	no effect	12	11
			0.05% day	1 year	no effect		
			1.25% day	1 year	50% died in 1 week; no lesions observed		
4	DBP	rats	0.25% (350-110mg/kg body weight	1 year	No effects (acute oral lethal dose = 8 g/kg)	14	11
			1.25%	1 year	50% fatal in 1 week; other 50% similar to controls. No gross or microscopic changes; DBP metabolized by pancreatic lipases		

TABLE 2 (Continued)

#	Compound	Species	Dose	Period	Effects	References Primary	 Secondary
5	DBP	rats	1.25% 0.25%	1 year	At 1.25% death occurred in five of ten animals during first week but the survivors at this level and all animals at 0.25% level showed no sign of clinical or tissue toxicity	14	9
6	DEHP	rat	500 mg/kg/day (oral)	4 generations	Normal reproduction. No anomalies during parturition or nursing	12	11
7	DEHP	rat	0.5% of diet (oral)	2 years	All body weights and organ weights unaffected. No pathological changes	15	11
8	DEHP	rat	0.13% of diet (oral) 0.4% 0.04%	2 years	No effects	16	11
9	DEHP	rat	0.5 mg/kg/day (oral)	6 months	No effects	13	11
10	DEHP	rat	0.5% of diet (oral) 0.1%	2 years	Mortality: no effect due to DEHP Body weight: no effect due to DEHP Food intake: no effect for first year; but 0.5% group ate only 75% of control group during second year No effect: 0.1% in rats for 2 years Organ weight: no difference, except for slight increase of liver and kidney with 0.5% diet Pathology: no effect	15	11

TABLE 2 (Continued)

#	Compound	Species	Dose	Period	Effects	Reference Primary	 Secondary
11	DEHP	rat	variable (oral)	13 weeks	At doses higher than 200 mg/kg/day, there was growth retardation, testicular degeneration and tubular atrophy	18	9
12	DEHP	rat	1.0 mg/kg/day (intravenous) 3.7 mg/kg/day	19 injections in 63 days	No effects on growth rate, organ weights, hematology or behavior. No biochemical or pathological changes	18	9
13	DEHP	rat	variable (oral)	Chronic unspecified	No effects below 60 mg/kg/day	15,17, 18	19
			200-400 mg/kg/day		Growth rates depressed; enlarged livers and kidneys		
14	DEHP	mouse	——— (inhalation)	1 hr., 3 times/ week for 12 weeks	No signs of unusual effects or behavior; autopsies revealed signs of diffuse chronic inflammation in the lungs similar to a burn	21	10
15	DEHP	mouse	——— (intraperitoneal)	11 weeks	Some cumulative effect is evidenced by the fact that the i.p. LD50 decreased from 25.41 ml/kg the first week to 3.06 ml/kg at the end of 11 weeks	20	10
16	DEHP	dog	5.0 gm/day (oral)	14 weeks	Slight loss in rate of weight gain; no other effects	15	11
17	DEHP	dog	0.13% of diet (oral)	1 year	No effects	16	11
18	Dimethyl Phthalate	unspecified	unspecified (inhalation)	repeated	Irritation of nasal mucous membranes and upper respiratory tract. May lead to CNS depression and eventual paralysis	24	10

TABLE 2 (Continued)

#	Compound	Species	Dose	Period	Effects	References	
						Primary	Secondary
19	DMP	rat	4%-8% in diet (oral)	2 years	Slight reduction in growth. Noticeable kidney damage at 8% level	24	10
20	DMP	rabbit	4 ml/kg (dermal)	90 days	50% of population died in 90 days. 90-day dermal LD50 = 4 ml/kg	20	10
21	Dioctyl Phthalate	mouse	(intraperitoneal)	11 weeks 5 days/wk	Some cumulative effects are evidenced by the fact that the LD50 decreased from 6.40 ml/kg the first week to 1.37 ml/kg after 10 weeks	20	10
22	Di mixed heptyl & nonyl phthalates	rat, mouse	0.125% in diet (oral)	90 days	Definitely no effect at 0.125%	22	11
			0.25%		Slight anemia at 0.25% and above		
			0.5%		Increased kidney and liver weights at 0.5% and above		
			1.0%		Growth retardation in males at 1%		
23	Diisodecyl Phthalate	rat, dog	1% in diet (oral)	14 weeks	No histological changes observed. Slightly elevated liver/body weight ratio in male dogs. Livers markedly heavier in rats	23	19

are cited, the author stated that "no carcinogenic characteristics were found by any of the investigators" (11).

Later in the same year, Autian stated that "no animal data have yet demonstrated that any of the phthalate esters act as carcinogenic agents. Likewise, their role as possible co-carcinogens has not been established" (10).

Dogs given 19 oral doses of 0.03 ml/kg of di-ethylhexyl phthalate followed by 221 doses of 0.06 ml/kg over the course of one year showed no carcinogenic effects (17, as reported in 10). However, no evaluation about the carcinogenicity of DEHP can be made because of the short experimental duration.

2.6 Mutagenicity

In 1973, Autian (10), in reviewing the literature on phthalate esters stated that "no published information is available on the mutagenic effects of phthalate esters." Since then, a dominant lethal assay study in mice has been reported (26), as described below.

Ten male mice were treated intraperitoneally with DEHP at one-third, one-half, and two-thirds of the acute LD50 dose (12.78, 19.17 and 29.56 ml/kg respectively). The results revealed significant reductions in mean live fetuses and mean implants per pregnancy which were indicative of a dominant lethal mutation for the compound

A bacterial mutagenesis study is reported in the abstract of a Japanese article. DEHP was reported to be non-mutagenic in bacterial tests. However, the monoester, which is a metabolite of DEHP, showed

DNA damage-provoking activity in Bacillus subtilis and mutagenicity in E. Coli (27).

2.7 Teratogenicity

Positive results were reported in three studies. One is a feeding study with mice, the other two are intraperitoneal studies using rats and chicks.

An abstract of a Japanese article (27) reports that DEHP was administered orally to pregnant mice at 1/12 - 1/3 of the LD50 dose, once a day during days 6-10 of gestation. Many fetal deaths were observed at higher doses on day 7. Very few deaths were recognized in the groups treated on days 9 and 10 even with the highest dose. A significant number of external and skeletal malformations were found in the group with 7.5 ml/kg on day 8.

The intraperitoneal study (28) in the rat was performed as follows: Relatively high (0.3 - 10.0 ml/kg) doses of several phthalate esters were injected intraperitoneally into pregnant Sprague-Dawley rats three times during gestation, on days 5, 10, and 15. Table 3 shows the numbers and precentages of resulting malformed embryos. Abnormalities noted included the absence of tails and eyes and twisted legs. Less dramatic skeletal anomalies were also noted.

Despite the high doses used in the rat experiment, the investigators believe that the major anomalies are impressive because of the unusual dose regime followed. Rat organogenesis begins at about day 8 and is, for many organ systems such as the brain and limb buds, complete by day

TABLE 3

GROSS AND SKELETAL MALFORMATIONS PRODUCED BY PHTHALATE ESTERS (28)

Treatment Groups	Volume Injected ml/kg	Number of Resorptions[a]	Number of Gross Abnormalities[b]	Number of Skeletal Abnormalities[c]
Untreated controls	None	0	0	0
Distilled water	10.00	4 (6.8%)	0	0
Normal saline	10.00	7 (11.5%)	1 (1.9%)	4 (14.3%)
Cottonseed oil	10.00	4 (6.8%)	1 (1.8%)	3 (10.7%)
	5.00	3 (6.4%)	0	0
Dimethyl phthalate	1.125	17 (32.1%)	4 (11.1%)	9 (75.0%)
	0.675	0	4 (7.5%)	6 (35.3%)
	0.338	21 (33.3%)	4 (9.5%)	4 (25.0%)
Dimethoxyethyl phthalate	1.245	55 (96.5%)	2 (100.0%)	2 (100.0%)
	0.747	52 (89.7%)	5 (83.3%)	4 (100.0%)
	0.374	16 (27.6%)	1 (2.4%)	13 (92.9%)
Diethyl phthalate	1.686	2 (3.6%)	0	13 (81.3%)
	1.012	0	0	8 (47.1%)
	0.506	28 (44.4%)	0	5 (26.3%)
Dibutyl phthalate	1.017	23 (36.5%)	0	8 (33.3%)
	0.610	2 (3.6%)	0	7 (24.1%)
	0.305	4 (7.3%)	0	6 (20.7%)
Diisolbutyl phthalate	1.250	16 (25.8%)	0	8 (33.3%)
	0.750	3 (5.5%)	2 (3.9%)	5 (17.2%)
	0.375	5 (9.6%)	0	4 (14.8%)
Butyl carbobutoxy-methyl phthalate	2.296	13 (24.1%)	1 (2.4%)	5 (21.7%)
	1.378	8 (14.5%)	1 (2.1%)	4 (16.0%)
	0.689	4 (7.8%)	0	4 (13.8%)
Dioctyl phthalate	10.00	5 (8.3%)	15 (27.3%)	0
	5.00	2 (3.8%)	8 (15.7%)	0
Di-2-ethylhexyl phthalate	10.00	15 (26.8%)	9 (22.0%)	0
	5.00	5 (8.2%)	0	0

a. Numbers in parentheses represent percent resorption based on total number of implantations.
b. Numbers in parentheses indicate percent gross abnormalities based on total number of fetuses.
c. Numbers in parentheses represent percent skeletal abnormalities based on total number of stained fetuses.

10. Thus, the injections on days 5, 10, and 15 would miss the critical period sought by most researchers in teratology. Another problem was the high incidence of dead (resorbed) fetuses which may have masked many abnormalities (28).

The chick study involved injection of several phthalate esters either into the yolk sac or allantoic cavity , or direct application to the chorioallantoin membrane of developing embryos. A syndrome of neural and musculo-skeletal anomalies was observed. Doses and stages of administration were not available at the time of this writing (29, 30 as reported in 31).

Besides teratogenic effects, phthalates have been found to have other reproductive effects. In a study by Peters and Cook (32), pregnant rats were injected with dibutyl or di-2-ethylhexyl phthalate at 2 or 4 ml/kg. Di-methyl phthalate was injected at 0.5, 1 or 2 ml/kg. DEHP prevented implantation in 7 out of 10 rats injected at 3, 6 and 9 days of gestation at 2 or 4 ml/kg. Excessive bleeding and maternal mortality were noted at parturition. DBP caused a 50% reduction in the number of young weaned per litter and a decrease in the number of implantations. DMP did not cause a significant decrease in the number of young weaned.

When labeled di-2-ethylhexyl and diethyl phthalates were administered to pregnant rats intraperitoneally, traces of the chemicals and/or metabolites were found in the maternal blood, the placenta, the amniotic fluid, and in the fetus. This suggests that the reports of teratogenesis and fetal deaths could be the result of the direct effect of phthalic esters on developing embryonic tissue (33).

2.8 Metabolic Information

Numerous articles describing absorption, distribution, metabolism and excretion of phthalate esters have appeared. Metabolism of alkyl phthalates may involve initial hydrolysis to monoester with subsequent side chain oxidation to the alcohol, ketone and acids. With the exception of dimethyl phthalate, phthalic acid has been found to be a minor metabolic component of the phthalate esters (34).

Butylglycol butyl phthalate, when treated in an isolated perfused rat liver system gives glycol phthalate as a metabolite (35) but DEHP is not metabolized by this system (36). In another study (37) DEHP was partially hydrolyzed to the monoester after oral administration to rats, and the residual alkyl moiety subjected to omega and omega-less-one oxidation. The alcohols can be further oxidized to the corresponding carboxylic acid or ketone and the acid may be subsequently subjected to beta oxidation. Hydrolysis of DEHP may occur in the liver or, alternatively, in the small intestine. *In vitro* studies indicate, however, that DEHP is hydrolyzed more rapidly by pancreatic lipase than by rat-liver homogenate (37).

In rats, intravenously administered DEHP appears to be extensively metabolized to water-soluble products (not well characterized) which are excreted primarily in the urine and feces. These results, according to the investigators, indicate that metabolism of DEHP by rats does not consist of simple de-esterification of the dialkyl ester, but rather that at least four chemically similar water soluble metabolites are formed (38).

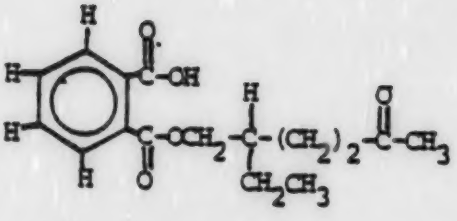
Rat, kidney, lung and liver tissue enzymatically hydrolyze DEHP *in vitro* to MEHP and 2-ethylhexanol. Liver mitochondria and microsomes have been strongly implicated as the site of this degradation. It would appear that a number of esterases or lipases are capable of hydrolyzing DEHP (according to the authors) (39).

A study (40) was made of the *in vitro* hydrolysis of the dimethyl, diethyl, di-n-butyl, di-n-octyl, di-(2-ethylhexyl), and dicyclohexyl esters by both hepatic (from rat, baboon and ferret) and intestinal preparations from various species (rat, baboon, ferret and man). Both the hepatic and intestinal preparations from these species hydrolyzed each of the phthalate diesters to their corresponding monoester derivatives. The results thus show a species similarity in the metabolism of phthalate diesters by man, a rodent, a non-rodent, and a nonhuman primate species. Furthermore, the authors state that their results suggest that orally ingested phthalate diesters would most probably be absorbed from the gut of these species primarily as the corresponding monoester derivative.

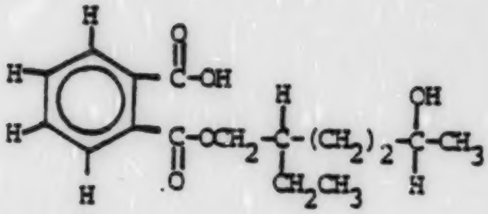
The metabolites appearing in the urine of rats fed with DEHP have been isolated and characterized (Table 4) by Albro *et al*. (34). Metabolites found were those expected from omega and omega-less-one oxidation of DEHP

TABLE 4

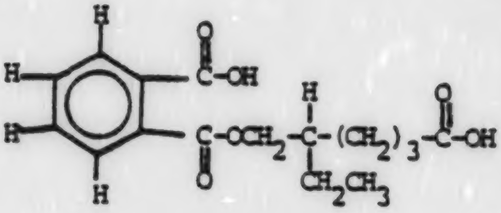
URINE METABOLITES OF DEHP FED TO RATS*



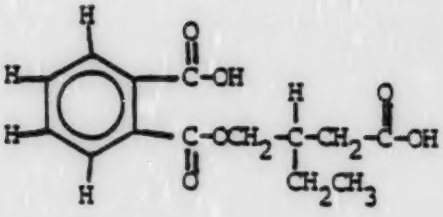
(1.)



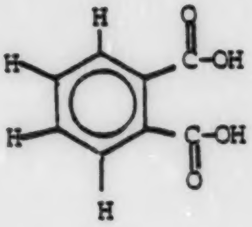
(2.)



(3.)



(4.)



(5.)

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*Albro, P.W., Thomas, R. and Fishbein, L. Metabolism of diethyehexyl phthalate by rats; Isolation and characterization of the urinary metobolities, J. Chromat. 76:321-330 (1973).

without attack on the aromatic ring. The metabolites do not form glucuronides. Free phthalic acid amounted to less than 3% of the urinary metabolites. The conclusion on glucuronides may require further investigation according to Carter et al. (39), since in another study (41) the ester glucuronide of the related compound monobutyl phthalate has been identified.

Albro and Moore (42) have identified (Table 5) rat urinary metabolites of orally administered dimethyl, di-n-butyl and di-n-octyl phthalates. Phthalic acid was a very minor metabolite except in the case of dimethyl phthalate. Hydrolysis to monoesters becomes more significant as they become more polar (methyl > butyl > n-octyl ≃ ethylhexyl). The remaining metabolites are those of subsequent oxidation of the side-chain to the alcohol, ketone and acid. The intact diester was excreted as a trace compound when dibutyl phthalate was fed to rats and as a significant component when dimethyl phthalate was similarly fed.

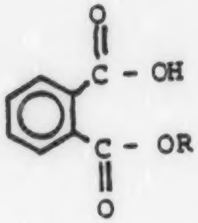
The metabolism of dibutyl phthalate (DNBP) has been recently investigated (43) in the rat. Phthalic acid, monobutyl phthalate, mono (3-hydroxybutyl) phthalate and mono (4-hydroxy butyl) phthalate have been identified as metabolites in the urine. Of a single oral dose of DNBP, 80-90% was metabolized and excreted in the urine within 48 hours.

2.9 Ecological Effects

The toxicity of phthalic acid esters in aquatic organisms has been evaluated by standard static and flow-through bioassay procedures. The 96-hr LC_{50} to scuds (Gammarus pseudolimnaeus) and crayfish (Orconectes nais) was 2.1 mg/l and > 10.0 mg/l, respectively (4). Acute toxicity of

TABLE 5

METABOLITES OF DIFFERENT PHTHALATE ESTERS*



Compound	Metabolites
Dimethyl phthalate	1. Free phthalic acid (14.4%)
	2. Monomethyl phthalate (77.5%)
	3. Dimethyl phthalate (8.1%)
Di-n-butyl phthalate	1. Phthalic acid
	2. Dibutyl phthalate (Intact)
	3. Mono-butyl phthalate
	4. $R = -CH_2COCH_3$
	5. $R = -(CH_2)_2CHOHCH_3$
	6. $R = -(CH_2)_3CH_2OH$
	7. $R = -(CH_2)_3COOH$
Di-n-octyl phthalate	1. Monooctyl phthalate
	2. Phthalic acid
	3. $R = -CH_2COOH$
	4. $R = -(CH_2)_2COOH$
	5. $R = -(CH_2)_3COOH$
	6. $R = -(CH_2)_4COOH$
	7. $R = -(CH_2)_5COOH$
	8. $R = -(CH_2)_6COOH$
	9. $R = -(CH_2)_7COOH$
	10. $R = -(CH_2)_6COCH_3$
	11. $R = -(CH_2)_6CHOHCH_3$
	12. $R = -(CH_2)_7CH_2OH$

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*Albro, P.W. and Moore, B. Identification of the metabolites of simple phthalate diesters in rat urine. J. of Chrom. 94:209-218 (1974).

di-n-butyl phthalate to aquatic organisms, as reported by Mayer and Sanders (4), is shown in Table 6. The 96-hr LC_{50} value of DEHP was greater than 10 mg/l for both fish and invertebrates (4).

TABLE 6

ACUTE TOXICITY OF DI-n-BUTYL PHTHALATE TO AQUATIC ORGANISMS

		LC_{50} value, mg/l	
Species	24 hrs.	48 hrs.	96 hrs.
Fathead minnow (*Pimephales promelas*)	-	1.49	1.30
Bluegill (*Lepomis macrochirus*)	1.23	0.73	0.73
Channel catfish (*Ictalurus punctatus*)	3.72	2.91	2.91
Rainbow trout (*Salmo gairdneri*)	-	-	6.47
Scud (*Gammarus pseudolimnaeus*)	7.00	-	2.10
Crayfish (*Orconetes nais*)	-	-	> 10.00

Alkyl phthalates have found their way into human food (45,46) in bovine and other tissues (47-49), air, soil (50), water (5,51) and aquatic organisms (5,6). The widespread occurence of the phthalate esters in aquatic ecosystems has also been reported by the U.S. Bureau of Sport Fisheries and Wildlife (6,44,59).

Fish from various locations in the United States have been analyzed for DEHP by Stalling *et al*. (53). Residue levels ranged from 0.2 to 10.0 μg/g on a whole fish basis, as shown in Table 7.

TABLE 7

PHTHALATE ESTER RESIDUES FOUND IN SELECTED SAMPLES FROM NORTH AMERICA

Source	Sample	Residue, ng/g (ppb)	
		DBP	DEHP
Mississippi and Arkansas (agriculture and industrial areas)	Channel catfish	Trace	1,000-7,500
Fairport National Fish Hatchery, Iowa (water supply from industrial area of Mississippi River)	Channel Catfish	200	400
	Dragonfly naiads	200	200
	Tadpoles	500	300
Black Bay, Lake Superior, Ontario (rural and industrial area)	Walleye	—	800
	Water	—	300
	Sediment	100	200
Hammond Bay, Lake Huron, Michigan (forested area)	Water	0.040	—
Lake Huron, Michigan	Water	—	5.0
Missouri River McBaine, Missouri	Water (turbid)	0.09	4.9

DEHP has also been found in catfish (6) in quantities greater than 3 ppm. 95 percent of the samples from Mississippi and Arkansas contained residue.

Phthalates in the Charles and the Merrimack rivers have been quantitively assessed by Hites (51) as shown in Table 8 below.

TABLE 8

PHTHALATE CONCENTRATION IN THE CHARLES RIVER

River Mile	Depth, ft	Phthalate concn, ppb
7	4	1.9, 1.8

TABLE 8 (Continued)

River Mile	Depth, ft	Phthalate concn, ppb
3	4	1.1, 1.1
1	4	0.88, 0.89
1	11	0.97, 0.98

Phthalate esters have been reported as being present in Kewda, tobacco leaf and lily of the valley, but the chemical structures of the esters have not been elucidated (10).

Analyses for phthalate esters by the FDA (58) indicate that the major contamination occurs in dairy products, but the level of contamination found was judged to be toxicologically insignificant.

Phthalate esters may interact with fulvic acid which is present in humic substances in soils and waters. The fulvic acid-phthalate ester complex is soluble in water, and thus the relatively insoluble esters can readily be solubilized and transported away from the original site of pollution (10,50). This phenomenon could possibly result in greater availability of phthalate esters to aquatic organisms (5).

Even though most of the phthalate esters have low volatility, they will volatilize from plastic materials, as for example, in the case of automobiles containing vinyl furnishings (10).

Effects of phthalate esters on aquatic organisms have been reported in the literature as follows:

Di-n-butyl phthalate (DNBP) slightly inhibits the hatching of brine shrimp eggs at 10.3 ppm. Diethyl phthalate inhibited hatching slightly at 61.5 ppm,and dimethyl phthalate did not inhibit hatching at 60.1 ppm (55, as reported in 54).

The no effect concentration for sac fry mortality was judged to lie between 5 and 14 ppb DEHP in water (54).

The effects of phthalate esters on aquatic organisms have demonstrated that brine shrimp are quite insensitive, but that sac fry of rainbow trout are more sensitive then adults during extended dynamic exposures (54).

DNBP was a heart rate depressor in goldfish at 1 ppm to 12 ppm, but DEHP did not produce this effect at 200 ppm. (56,57, as reported in 54).

DEHP did not affect the growth rate of fathead minnows during 56 days of exposure at concentrations as high as 62 ppb, but DEHP was accumulated 115 to 886-fold from the water (54).

DEHP and DNBP were fed to ring doves at 10 ppm in the diet. No effect due to DEHP was observed, but with DNBP, egg shell thickness was decreased by 10% and the rate of water loss from the egg was decreased by 23%. When the doves were returned to a normal diet, the eggshell thickness rapidly returned to normal (54).

Mayer et al. (5) reported that a concentration of only 3 μg/l of DEHP in the water was sufficient to significantly decrease growth and reproduction of the crustacean Daphnia magna.

DEHP is reported (4) to be detrimental to the reproduction of aquatic organisms at low concentrations. Waterfleas continuously exposed to 3, 10, and 30 μg/l of DEHP for a complete life cycle (21 days) showed reduced reproduction. Total production of offspring was inhibited by 60, 70, and 83% in the respective treatment levels.

The effects of DEHP on reproduction in Zebra fish (Brachydamio rerio) and guppies (Poecilia reticulatus) were determined with a 90-day dietary exposure (4). The number of spawns was greater in the treated Zebra fish, but the control fish produced more eggs per spawn than those fish exposed to DEHP. Fry survival was significantly reduced and the least number of guppy fry were born to parents fed DEHP. An 8 percent incidence of abortions was noted, as shown in Table 9 below.

TABLE 9

REPRODUCTION IN ZEBRA FISH (BRACHYDAMIO RERIO)
AND GUPPIES (POECILIA RETICULATUS)

Species	Reproductive variable	DEHP Concentration mg/g 0	50	100
Zebra fish	Number of spawns	6	8	14
	Eggs per spawn	20.3	15.2	10.1
	Percent fry survival	51.1	31.7	11.5
Guppies	Fry per female	33	----	29
	Percent abortions	0	----	8

2.10 Current Testing

Di(2-ethylhexylphthalate) (NCI #C52733) is currently being tested by NCI in rats and mice by feeding (G12).

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CHLORINATED BENZENES, MONO- AND DI-

TABLE OF CONTENTS

Page

Overview III-1

Part I - General Information

Chlorobenzene III-3

m-Dichlorobenzene III-5

o-Dichlorobenzene III-7

p-Dichlorobenzene III-10

Summary of Characteristics III-13

Specific References III-14

Part II - Biological Properties

Chlorobenzene

2.1 Bioaccumulation III-15

2.2 Contaminants and Environmental Degradation or Conversion Products III-15

2.3 Acute Toxicity III-17

2.4 Other Toxic Effects III-18

2.5 Carcinogenicity III-19

2.6 Mutagenicity III-19

2.7 Teratogenicity III-20

2.8 Metabolic Information III-20

2.9 Ecological Effects III-21

2.10 Current Testing III-22

References III-23

Page

Part II - Biological Properties (Continued)

o-Dichlorobenzene

2.1 Bioaccumulation III-26

2.2 Contaminants and Environmental Degradation or Conversion Products III-27

2.3 Acute Toxicity III-28

2.4 Other Toxic Effects III-29

2.5 Carcinogenicity III-30

2.6 Mutagenicity III-31

2.7 Teratogenicity III-32

2.8 Metabolic Information III-32

2.9 Ecological Effects III-32

2.10 Current Testing III-34

References III-35

p-Dichlorobenzene

2.1 Bioaccumulation III-37

2.2 Contaminants and Environmental Degradation or Conversion Products III-38

2.3 Acute Toxicity III-39

2.4 Other Toxic Effects III-40

2.5 Carcinogenicity III-42

2.6 Mutagenicity III-43

2.7 Teratogenicity III-43

2.8 Metabolic Information III-44

2.9 Ecological Effects III-45

2.10 Current Testing III-46

References III-47

CHLORINATED BENZENES, MONO- AND DI-

AN OVERVIEW

This category consists of monochlorobenzene and o-, m-, and p-dichlorobenzene. Monochlorobenzene and o- and m-dichlorobenzenes are colorless liquids while p-dichlorobenzene is a volatile white crystalline material. All of these compounds are insoluble in water but soluble in major organic solvents.

In 1976, over 325 million pounds of monochlorobenzene, 48 million pounds of o-dichlorobenzene and 36 million pounds of p-dichlorobenzene were produced. Chlorinated benzenes are used in solvent applications, industrial processes and many consumer products.

In the NOHS Survey of Occupational Exposure, the monochloro-, p-dichloro- and o-dichloro- benzenes ranked 195, 383, and 114, respectively, out of approximately 7000 agents; over a million workers are believed to be exposed to them. Nearly 100 million pounds of the o- and p-dichlorobenzenes are estimated to be released annually into the environment. The release rate for monochlorobenzene was not found.

Chlorinated benzenes have been detected in the environment. Their potential for bioaccumulation is considered great owing to their high octanol-water partition coefficients and the stability and low reactivity of the molecule. Chlorinated benzenes mainly give phenolic metabolites which are usually excreted as glucuronides, sulfate or mercapturic acid conjugates.

Liver, kidney, respiratory and neurological effects have been observed after exposure to chlorinated benzenes. There are no adequate studies available on which to evaluate the carcinogenicity of chlorinated benzenes, but an association has been reported between exposure to the dichlorobenzenes and leukemia. No conclusion can be drawn from current mutagenicity data on chlorinated benzenes, and no information on the teratogenicity of these chemicals is available.

CHLORINATED BENZENES (MONO- AND DI-)

PART I

GENERAL INFORMATION

I. Chlorobenzene

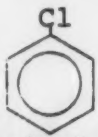
1.1 **Identification**

CAS No.: 000108907
NIOSH No.: CZ01750

1.2 **Synonyms and Trade Names**

Monochlorobenzene; phenyl chloride; benzene chloride; chlorbenzene; chlorbenzol; MCB (G16)

1.3 **Chemical Formula and Molecular Weight**



C_6H_5Cl Mol. Wt. 112.56 (G22)

1.4 **Chemical and Physical Properties**

1.4.1 Description: Colorless, volatile liquid; almond-like odor; flammable (G21)

1.4.2 Boiling Point: 132° C (G22)

1.4.3 Melting Point: -45.6° C (G22)

1.4.4 Absorption Spectrometry:

$$\lambda_{max}^{alcohol} = 245,251,258,264,272\text{nm}$$

$$\log \epsilon = 1.95,2.34,2.13,2.45,2.32$$ (G22)

1.4.5 Vapor Pressure: 10 mm at 22.2° C (G22)

1.4.6 Solubility: Insoluble in water; Very soluble in benzene, chloroform, carbon tetrachloride and carbon disulfide; Soluble in all proportions in alcohol and ether

1.4.7 Octanol/Water Partition Coefficient:

$$\text{Log } P_{oct} = 2.84$$ (G36)

1.5 Production and Use

1.5.1 Production:

576.749 Million lbs	(1966)	
484.914 Million lbs	(1970)	
306.030 Million lbs	(1975)	
329.072 Million lbs	(1976)	(G24)

1.5.2 Use:

In manufacture of phenol, chloronitrobenzenes, aniline; as a solvent carrier for methylene diisocyanate; as a solvent for paints; as a pesticide intermediate; as a heat transfer medium (G21,G23)

Quantitative Distribution of Uses:

	Percent
Intermediate (including *o*- and *p*-nitrochlorobenzene)	35
Solvent	30
DPO and derivatives	10
Rubber intermediate	10
DDT, silicones, isocyanates and others	15
	100

(2)

Consumer Product Information:

Chlorobenzene is present in: marine primer (G35)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure:

Rank: 195

Estimated no. of persons exposed: 1,093,000

(G29)

1.7 Manufacturers

Allied Chemical Corp.
Dow Chemical Co.
Monsanto Co.
Montrose Chemical Corp. of Calif.
PPG Industries, Inc.
ICC Solvent Co., Inc.
Standard Chlorine Chemical Co.

(G25,1)

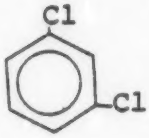
II. m-Dichlorobenzene

1.1 **Identification** CAS No.: 000541731
NIOSH No.:

1.2 **Synonyms and Trade Names**

1,3-Dichlorobenzene (G21)

1.3 **Chemical Formula and Molecular Weight**



$C_6H_4Cl_2$ Mol wt. 147.01

(G22)

1.4 **Chemical and Physical Properties**

1.4.1 **Description**: Colorless liquid (G21)

1.4.2 **Boiling Point**: 173° C (G22)

1.4.3 **Melting Point**: -24.7° C (G22)

1.4.4 **Absorption Spectrometry**:

$$\lambda_{max}^{alcohol} = 250, 256, 263, 270, 278 \text{ nm}$$

$$\log \epsilon = 1.90, 2.15, 2.40, 2.52, 2.43$$

(G22)

1.4.5 **Vapor Pressure**: 1 mm at 12.1° C (G22)

1.4.6 **Solubility**: Insoluble in water;
Soluble in alcohol, ether, and benzene;
Soluble in all proportions in acetone, ligroin and carbon tetrachloride

(G22)

1.4.7 **Octanol/Water Partition Coefficient**

$$\text{Log } P_{oct} = 3.38$$

(G36)

1.5 Production and Use

1.5.1 **Production**:

No information found in sources searched

1.5.2 **Use**: As a fumigant and insecticide

(G21)

1.6 Exposure Estimate

1.6.1 **Release Rate**:

No information found in sources searched

1.6.2 **NOHS Occupational Exposure**

Rank:

No information found in sources searched

Estimated no. of persons exposed:

No information found in sources searched

1.7 Manufacturers

Aceto Chemical Co., Inc.
American Hoechst Corp.
Mitsubishi International Corp.
Standard Chlorine Chemical Co., Inc.

(G37)

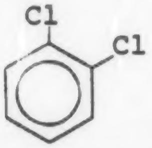
III. *o*-Dichlorobenzene

1.1 Identification CAS No.: 000095501
NIOSH No.: CZ45000

1.2 Synonyms and Trade Names

Chloroben; cloroben; DCB; *o*-dichlorobenzene; *o*-dichlor benzol; 1,2-dichlorobenzene; Dizene; Dowtherm E; ODB; ODCB; ortho-dichlorobenzol (G16)

1.3 Chemical Formula and Molecular Weight



$C_6H_4Cl_2$ Mol. Wt. 147.01 (G23)

1.4 Chemical and Physical Properties

1.4.1 Description: Colorless liquid, pleasant odor; a mixture of isomers containing at least 85% *o*- and varying percentages of *p*- and *m*- (G21)

1.4.2 Boiling Point: 180.5° C (G22)

1.4.3 Melting Point: -17.0° C (G22)

1.4.4 Absorption Spectrometry:

$$\lambda_{max}^{alcohol} = 250, 256, 263, 270, 277 \text{ nm};$$

$$\log \epsilon = 1.98, 2.13, 2.36, 2.44, 2.37$$

(G22)

1.4.5 Vapor Pressure: 1 mm at 20° C (G22)

1.4.6 Solubility: Insoluble in water;
Soluble in alcohol, ether, benzene;
Soluble in all proportions in acetone, ligroin, carbon tetrachloride (G22)

1.4.7 Octanol/Water Partition Coefficient:

$$\text{Log } P_{oct} = 3.38$$ (G36)

1.5 Production and Use

1.5.1 Production:

51.386	Millions lbs	(1966)	
66.219	Millions lbs	(1970)	
54.679	Millions lbs	(1975)	
48-594	Millions lbs	(1976)	(G24)

1.5.2 Use: In manufacturing of 3,4-dichloroaniline; as a solvent for a wide range of organic materials and for oxides of nonferrous metals; as a solvent carrier in production of toluene diisocyanate; in the manufacture of dyes; as a fumigant and insecticide; in degreasing hides and wool; in metal polishes; in industrial odor control; in drain cleaners

(G21)

Quantitative Distribution of Uses:

	Percent
Organic synthesis, mainly for pesticides	53
Toluene diisocyanate process solvent	20
Solvent, including paint removers and engine cleaners	15
Dye manufacture	8
Miscellaneous	4
	100

(G25)

Consumer Product Information:

o-Dichlorobenzene is present in:

radiator cleaner
leather dye
conditioner for lawn mower engines (G35)

1.6 Exposure Estimates

1.6.1 Release Rate: 27.0 Million lbs

1.6.2 NOHS Occupational Exposure:

Rank: 114

Estimated no. of persons exposed: 1,978,000

(G29)

1.7 Manufacturers

Allied Chemical Corp.: Specialty Chemicals Div.
Dow Chemical Co.
Monsanto Co.
PPG Industries, Inc.
Montrose Chemical Corp.
ICC Industries, Inc.
Standard Chlorine Chemical Co.
Chemical Products Corp.
Specialty Organics

(G24,1)

CHLORINATED BENZENES (MONO- AND DI-)

IV. p-Dichlorobenzene

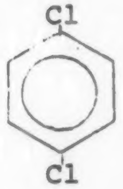
1.1 **Identification** CAS No.: 000106467
NIOSH No.: CZ45500

1.2 Synonyms and Trade Names

Di-cloricide, p-Chlorobenzol; 1,4-dichlorobenzene; Paracide; Paradi; Paradow; Paramoth; PDB; PDCB; Santichlor

(G16)

1.3 Chemical Formula and Molecular Weight



$C_6H_4Cl_2$ Mol. Wt. 147.01

(G23)

1.4 Chemical and Physical Properties

1.4.1 **Description:** White crystals; volatile (sublimes readily); penetrating odor (G21)

1.4.2 **Boiling Point:** 174° C (G22)

1.4.3 **Melting Point:** 53.1° C (G22)

1.4.4 **Absorption Spectrometry:**

$$\lambda_{max}^{alcohol} = 258,\ 266,\ 273,\ 280\ \text{nm};$$

$$\log \epsilon = 2.24,\ 2.46,\ 2.60,\ 2.51$$

(G22)

1.4.5 **Vapor Pressure:** 0.4 mm at 25° C (1)

1.4.6 **Solubility:** Insoluble in water;
Soluble in ether, benzene, carbon disulfide, chloroform;
Soluble in all porportions in alcohol, acetone

(G22)

1.4.7 Octanol/Water Partition Coefficient

Log $P_{oct} = 3.39$ (G36)

1.5 Production and Use

1.5.1 Production:

66.307 Million lbs	(1966)	
69.606 Million lbs	(1970)	
45.755 Million lbs	(1975)	
36.699 Million lbs	(1976)	(G24)

1.5.2 Use:

As a moth repellent, general insecticide, germicide, space odorant; in the manufacture of 2,5-dichloroaniline and dyes; as an intermediate; in pharmacy and agriculture (fumigating soil)

(G21)

Quantitative Distribution of Uses:

	Percent
Space odorant	50
Moth control	40
Miscellaneous	10
	100

(G25)

Consumer Product Information:

Category	Total no. of p-dichlorobenzene containing products	$\frac{\text{No. of p-dichlorobenzene products in category}}{\text{total no. of products in category}} \times 100$
Cleaning agents and compounds	3	0.2%
Chemical deodorizers	51	16.0%

The 54 products surveyed contained an average of 85.3% p-dichlorobenzene (G27)

1.6 Exposure Estimates

1.6.1 Release Rate: 71.0 Million lbs (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 383

Estimated no. of persons exposed: 544,000*

* rough estimate (G29)

1.7 Manufacturers

Allied Chemical Corp.: Specialty Chemicals Div.
Dow Chemical Co.
Dover Chemical Co.
PPG Industries, Inc.
Monsanto Co.
Montrose Chemical Corp.
Standard Chlorine Chemical Co.
Specialty Organics

(G24,1)

CHLORINATED BENZENES (MONO- AND DI-)

SUMMARY OF CHARACTERISTICS

Name	Solubility	Log P_{oct}	Estimated Environmental Release (Million lbs)	Production (Million lbs)	Estimated no. of persons exposed (occupational)	Use
Benzene, chloro-	i in H_2O; vs in bz, chl, CCl_4, CS_2; ∞ in alc. and eth.	2.84	*	576.729 (1966) 484,914 (1970) 306.030 (1975) 329.072 (1976)	1,093,000	Mfg. of phenol; chloronitrobenzene, aniline; solvent carrier for methylene diisocyanate; solvent for paints; pesticides intermediate; marine primer; heat transfer medium
Benzene, o-dichloro	i in H_2O; s in alc, eth, bz; ∞ in ace, lig, CCl_4	3.38	27.0	51.386 (1966) 66.219 (1970) 54.679 (1975) 48.594 (1976)	1,978,000	Mfg. of 3,4-dichloroaniline; solvent for wide range of org. mats. and for oxides of nonferrous metals; solvent carrier in prod. of toluene diisocyanate; dye mfg; fumigant and insecticide; degreasing hides and wool; metal polishes; industrial odor control
Benzene, p-dichloro	i in H_2O; s in eth, bz, CS_2, chl; ∞ in alc, ace.	3.39	71.0	66,307 (1966) 69.606 (1970) 45.755 (1975) 36.699 (1976)	~ 544,000	Moth repellent; general insecticide; germicide; space odorant; mfg. of 2,5-dichloroaniline; dyes; intermediates; pharmacy; agriculture (fumigating soil)
Benzene, m-dichloro	i in H_2O; s in alc, eth, bz; ∞ in ace, lig, CCl_4	3.38	*	*	*	Fumigant ; insecticide

* No information found in sources searched.

CHLORINATED BENZENES (MONO- AND DI-)

SPECIFIC REFERENCES FOR PART I

1. EPA. 560/2-77-004, Investigation of selected potential environmental contaminants: Halogenated benzenes. Office of Toxic Substances, U.S. Environmental Protection Agency, (1977).
2. Chemical Profile, Monochlorobenzene, Chemical Marketing Reporter, October 31, 1977.

CHLOROBENZENE

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

Chlorobenzene was tested for bioaccumulation in a model aquatic ecosystem by Lu and Metcalf (1). The model ecosystem contained: 300 Daphnia; 200 4th instar mosquito larvae; 6 snails; strands of algae; and miscellaneous plankton. Radio-labelled (^{14}C) chlorobenzene was added to the water phase, and three fish were added one day later. When an additional day had passed, the ecosystem components were extracted for chlorobenzene. Biological magnification values found were as follows: fish, 645; mosquito larvae, 1292; snail, 1313; Daphnia, 2789; and algae, 4185.

In a study of chlorinated benzene content of human adipose tissue of residents of the Tokyo area, chlorobenzene was less than 10 ppb in all samples. Exposure rates were not estimated (2,3).

That chlorobenzene bioaccumulates is consistent with its high octanol-water partition coefficient and the stability and low reactivity of the molecule.

2.2 Contaminants and Environmental Degradation or Conversion Products

The BOD of chlorobenzene is reported as 1% of theoretical (G15). This result indicates resistance to biodegradation. At ordinary temperature and pressure it is unaffected by the presence of air, moisture, or light and shows no tendency to dechlorination (G17).

Possible contaminants (formed during manufacture of the chemical) are o- and p-dichlorobenzene (G17).

The following reports show that chlorobenzene degrades slowly in the environment:

The chemical is oxidized to 3-chlorocatechol by Pseudomonas putida but oxidation occurs only if the organism is initially grown on toluene for 15 hr and then on the chemical for 20 hr (5, as reported in 4). It appears that P. putida can oxidize chlorobenzene only if it is already adapted to an aromatic carbon source.

The biodegradability index (ratio of polar products of degradation to nonpolar products) ranges from 0.014 to 0.063, which again indicates substantial resistance to biodegradation. In mosquito fish, the biodegradability index of 0.014 for chlorobenzene was between that of DDT (0.012) and aldrin (0.015) (1).

The BOD with sewage microflora was only 0.03 g/g for chlorobenzene (compared with 1.20g/g for benzene),which likewise shows a very slow rate of degradation for the compound (6,as reported in 4).

Owing to its high vapor pressure (15.5 mm at 30°C), chlorobenzene will volatilize when released to the environment, even when released in water (7, as reported in 4). Its fate in the atmosphere is, therefore, of special interest. In a study of rate of degradation of the chemical in a simulated atmosphere (8, as reported in 4), it was found that the chemical decomposed relatively slowly.

Hydrolysis of chlorobenzene (to phenols) does not seem likely owing to its low water solubility and the low reactivity of aromatic chlorine.

All of the foregoing data are consistent in showing chlorobenzene to be a non-reactive, persistent chemical in the environment, both in water and air.

2.3 Acute Toxicity

The NIOSH Registry of Toxic Effects of Chemical Substances (G16) reports the following acute toxicity data for chlorobenzene:

Parameter	Dosage (mg/kg)	Animal	Route
LD50	2910	rat	oral
LDLo	4000	rat	s.c.
LD50	2830	rabbit	oral

The EPA report on halogenated benzenes (4) gives the following acute toxicity data for this compound:

Parameter	Dosage (mg/kg)	Animal	Route
LD50	1445	mouse	oral
LD50	2390	rat	oral
LD50	2250	rabbit	oral
LD50	5060	guinea pig	oral
LC50	20	mouse	inhal.
LC50	0.05	guinea pig	inhal.

Acute poisoning in laboratory animals is characterized by symptoms primarily originating in the nervous system, including hyperexcitability, restlessness, muscle spasms or tremors followed by varying degrees of CNS depression. Respiratory failure is the most frequent cause of death (9, as reported in 4). Subcutaneous injection of 4-5 g/kg of chlorobenzene in rats caused no immediate effects, but resulted in death within a few days. Autopsy revealed liver and kidney necrosis. Larger doses produced CNS depression and acute ataxia. 7-8 g/kg of chlorobenzene was fatal to rats in a few hours, (10, as reported in 4). Inhalation of 20 mg/l of chlorobenzene in rabbits was fatal for all animals in comparison with 30 mg/l for benzene (11, as reported in 4). Exposure to chlorobenzene vapor in humans causes headaches, irritation of the eyes and upper respiratory tract, numbness and eventual loss of consciousness (9, as reported in 4).

2.4 Other Toxic Effects

Functional disorders of circulatory organs in workers employed in the production of chlorobenzene have been reported (12). Symptoms included pain in the area of the heart, bradycardia, irregular variations in EKG, and decreased contractile function of the myocardium. Specific alterations which occurred in external respiration caused secondary disorders in the circulatory organs (12). In the majority of cases, exposure lasted over three years and did not exceed the maximum allowable concentration.

Rats exposed to 1.0 mg/m^3 of chlorobenzene, 24 hours/day for approximately 2 months experienced liver, lung and kidney damage, blood dyscrasias, and a change in the regulating influence of the CNS (13, as reported in 4).

Inhalation exposure to chlorobenzene (0.1-1.5 mg/l) in guinea pigs for 2 months decreased the activity of red cell enzymes (14, as reported in 4). Repeated subcutaneous injection of 0.9 mg/kg chlorobenzene in rabbits resulted in liver and kidney damage, blood dyscrasia and CNS depression. Oral administration of 0.001-0.1 mg/kg chlorobenzene to male white rats daily for five months caused CNS depression and the higher dose caused liver and kidney damage (15, as reported in 4).

Chlorobenzene (orally administered, 250 mg/kg for 3 days) caused a doubling in rat liver δ-aminolevulinic acid synthetase activity, the rate-limiting factor in the enzymatic synthesis of porphyrins, and caused porphyria (4). Administration of 200-400 mg/kg/day of chlorobenzene resulted in approximately a 2-fold increase in glucuronyl transferase activity in the rat (18, as reported in 4).

Covalent binding of chlorobenzene metabolites to rat liver protein *in vivo* was significantly stimulated by phenobarbital, an inducer of microsomal mixed-function oxidase activity. This stimulation was blocked by SKF-525A, an inhibitor of microsomal metabolism (19). In contrast, *in vivo* binding to rat lung protein was either not affected or was inhibited by phenobarbital (20). A correlation has been observed between the extent of covalent binding of halogenated benzene metabolites in protein *in vitro* and *in vivo*, and the severity of liver necrosis. In contrast to fluorobenzene, both protein binding and liver necrosis were extensive for chlorobenzene (14).

The Threshold Limit Value (TLV) recommended by the ACGIH (1976) is 75 ppm (350 mg/m^3) (G11).

2.5 Carcinogenicity

No data on the carcinogenicity of chlorobenzene were found in the searched literature. Pentachlorobenzene has been reported to cause tumors in mice (16, as reported in 4).

2.6 Mutagenicity

Spores of the vitamin B_{12}-deficient mutant *Streptococccus antibioticus 400* were treated with chlorobenzene (0.05 and 0.1 ml).

After 24 hours, all spores were dead. At six hours, the maximum yield of back mutations observed exceeded the controls by a factor of 187 (low dose) and 1400 (high dose) (17, as reported in 4).

Chlorobenzene caused chromosomal damage and mitotic inhibition in root tips of higher plants.

Chlorobenzene was not found to be mutagenic in the fungus Aspergillus ridulans (1).

2.7 Teratogenicity

No data on the teratogenicity of chlorobenzene were found in the searched literature. Evidence has been presented that pentachlorobenzene is teratogenic (4).

2.8 Metabolic Information

Chlorobenzene is oxidized mainly to 4-chlorophenol and 4-chlorocatechol and excreted in the urine as sulfate, mercapturic acid and glucuronic acid conjugates. About 25% of an oral dose of 0.5 g/kg in rabbits was eliminated via expiration and the remainder was excreted by the kidneys in 1-2 days. Approximately equal quantities (32%) of 4-chlorophenol and 4-chlorocatechol have been isolated from a 24-hour urine specimen in man and a smaller percentage (16%) was recovered as 4-chlorophenyl mercapturic acid. In contrast, the percent of dose recovered as mercapturic acid conjugate in the monkey, dog, mouse and rat was significantly higher (> 40%) (4).

Direct evidence for the generation of a reactive epoxide intermediate from bromobenzene (4) suggests that a similar intermediate is formed in the metabolism of other halogenated benzenes, which may be the metabolite that reacts with cellular proteins.

2.9 Ecological Effects

Chlorinated benzenes have been detected in waste waters, drinking waters, rivers and lakes as well as in the soil (4). From an EPA study that estimated loss of materials during batch manufacture of chlorobenzene by a plant (presumed to be typical) (21, as reported in 4), the following are estimates of chemicals vented to the environment annually, assuming the figures given for the plant selected apply to the entire U.S. production of chlorobenzene, about 400 million lb/year:

Chemical	Quantity Vented, lb.	Destination
Hydrogen chloride	560,000	air
Monochlorobenzene	352,000	water stream
Dichlorobenzenes	1,480,000	water stream

Usage of chlorobenzene as an intermediate will result in additional venting of the chemical to the environment. For example, 0.02 - 0.3 mg/l was found in the atmosphere of a new DDT manufacturing plant in Romania (22, as reported in 4); this indicates leaks in piping and inadequate ventilation are occurring even in new plants. Loss from scrubbers is another source of environmental contamination (23, as reported in 4).

Murray State College, Kentucky has reported chlorobenzene (and higher chlorinated benzenes) in textile finishing plant effluents (24, as reported in 4). The chemical has been found in U.S. drinking water, with the highest level being 5 μg/l (25, as reported in 4). It has also been found in 9 of 10 cities surveyed: in ground water, in supposedly uncontaminated upland water, and in waters contaminated by industrial, municipal or agricultural wastes (25, as reported in 4).

In a 15-day static test of chlorobenzene (at 17 - 20°C) on aquatic organisms serving as food for freshwater fish, 25 mg/l was toxic to saprophytic microflora (based on BOD) and nitrogen-fixing bacteria (based on nitrification processes); 1.0 mg/l was toxic to crayfish and *Daphnia magna*; and 20 mg/l was toxic to the oligochaetes *Limnodrilus hoffmeister* and *Tubifex tubifex*, and the chironomid larvae *Stictochironomus*. Crayfish were tolerant of 0.5 mg/l which was the concentration suggested as permissible (26).

Of four species of fish--fathead minnows (*Pimephales promelas*), bluegill (*Lepomis machrochirus*), goldfish (*Carassius auratus*) and guppies (*Lebistes reticulatus*)--tested at 25°C, bluegills were the most sensitive to chlorobenzene with 24-, 48-, and 96-hr TLms of 24.0 mg/l (27).

2.10 Current Testing

Chlorobenzene (NCI #C554886) has been tentatively selected for long-term bioassay testing by the NCI (G12).

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o-DICHLOROBENZENE

2.1 Bioaccumulation

The propensity for o-dichlorobenzene to bioaccumulate is considered great. The log of the octanol/water partition coefficient is 3.38 (G15). The halogenated aromatic structure confers stability on the molecule, which helps ensure its environmental persistence and its resistance to biodegradation.

Although specific test data on the compound are not available, indications are very strong, from data on closely related compounds, that o-dichlorobenzene will bioconcentrate. For example, blood and fat samples taken from inhabitants of the Tokyo, Japan area were found to contain the closely related para isomer of the compound; fat levels were 0.2-11.7 µg/g and blood levels (on whole blood basis) 8-12 µg/ml (1). In a small model aquatic ecosystem, the following ecological magnification factors were observed for chlorobenzene with the species indicated: mosquito fish 645, mosquito larvae 1292, snails 1313, Daphnia 2789, and algae 4185. The log octanol/water partition ratio of o-dichlorobenzene (3.38) is much higher than that of chlorobenzene (2.176) (2) suggesting a greater potential for bioaccumulation. It has also been observed that the para isomer of the compound can bioconcentrate in trout muscle (3). Dichlorobenzene has been identified in samples of sprat (*Clupea sprattus*) (4). A mixture of 7 chlorinated hydrocarbons (including o-dichlorobenzene), all known to be pollutants of Rhine water, when administered orally to rats, was found in the fat at levels 50 to 100 times that in the administered dose. Generally, highly chlorinated aromatic compounds accumulate to a greater extent than less-chlorinated aromatics (5).

2.2 Contaminants & Environmental Persistence

The technical grade contains 1.3% of the meta- and para- isomers and the crude grade contains 17% of the meta- and para- isomers (G9). Other impurities are 1,2,4-trichlorobenzene, monochlorobenzene, and chlorotoluene (G14).

o-Dichlorobenzene is unreactive toward peroxides in water and ozone in air, but is very reactive to hydroxyl radical; the $t_{1/2}$ is about 3 days (G14). Products of these reactions were not given. The affinity of the compounds for fatty tissues would tend to result in bioaccumulation and, therefore, increased persistence in the environment. However, only traces of the chemical have been detected in water effluents or supplies (see Section 2.9). The compound has been reported to be degraded by sewage sludge organisms (7, as reported in 6).

However, this process is probably very slow since the BOD of chlorobenzene was 0.03 g/g (8, as reported in 6) and it was noted that the introduction of chlorine atoms in an organic molecule lowered the BOD; i.e., the BOD of the dichlorobenzene should be less than the 0.03 g/g of chlorobenzene. o-Dichlorobenzene at levels up to 300 mg/l appears to codistil from water readily since it volatilized completely from aerated distilled water in less than 4 hours (9, as reported in 6). Without aeration the chemical volatilized in less than 3 days. Once in air, the chemical is subject to OH attack. Degradation products in water were not detected.

2.3 Acute Toxicity

The NIOSH Registry of Toxic Effects of Chemical Substances (G16) reports the lowest lethal concentrations in air (LCLo) and lowest lethal dosage by other routes (LDLo) for ≥ 99% o-dichlorobenzene as follows:

Parameter	Dosage	Animal	Route
LCLo	707 ppm/4H	rat	inhalation
LCLo	800 ppm/24H	guinea pig	inhalation
LDLo	2000 mg/kg	guinea pig	oral
LDLo	330 mg/kg	rabbit	intravenous
LDLo	520 mg/kg	mouse	intravenous

The EPA report Investigation of Selected Potential Environmental Contaminants: Halogenated Benzenes (6) gives the oral LD50 for several experimental animals as follows:

Animal	LD50 (mg/kg)
mouse	2000
rat	2138
rabbit	1875
guinea pig	3375

Acute exposure of sewage workers to o-dichlorobenzene effluents from a dry cleaning establishment above the plant resulted in eye and upper respiratory tract irritation and vomiting. (10, as reported in 6).

o-Dichlorobenzene is toxic in many species of mammals, the extent of toxicity depending on the species and route of administration. Intravenous administration of 0.25 - 0.50 ml/kg body weight to rabbits was fatal within 24 hours and 1.00 ml/kg was fatal within 20 seconds (11, as reported in 6). Exposure of dogs to o-dichlorobenzene vapor at 2 ml/m^3 (0.04%) did not result in adverse effects but 4 ml/m^3 (0.08%) produced somnolence (12, as reported in 6). Exposure of mice to a similar concentration of o-dichlorobenzene resulted in CNS stimulation for about twenty minutes followed by CNS depression, muscular twitching, slow and irregular respiration, cyanosis near the end of an hour and death within 24 hours. Rats and guinea pigs appear more resistant than mice (12, as reported in 6). The clinical symptoms of acute poisoning in rats are hyperemia, increased salivation, ataxia, paraparesis, paraplegia and dyspnea. Similar symptoms of acute poisoning are observed in rabbits including hyperemia of visible mucous membranes, increased salivation and lacrimination, ataxia, paraparesis, paraplegia, initial excitation followed by sleepiness and dyspnea (14).

2.4 Other Toxic Effects

Daily administration of 18.8 - 188 mg/kg of o-dichlorobenzene to rats via stomach tube 5 days/week for 192 days did not produce any adverse effects. At 376 mg/kg, positive findings consisted of a moderate increase in liver and kidney weight, and a slight decrease in spleen weight. Microscopic examination of the liver revealed slight to moderate cloudy swelling (13). Repeated 7 hour exposures to 93 ppm of o-dichlorobenzene in air for 6-7 months had no adverse effects in the rat, guinea pig, rabbit and monkey (13). o-Dichlorobenzene was absorbed through the skin and was toxic after repeated cutaneous administration. Subcutaneous injection produced localized edema and necrosis of adjoining tissue. Repeated subcutaneous injections in rats resulted in blood dyscrasias characterized by agranulocytosis, with little or no effect on red blood cells (12 as reported in 6).

Sensitization to o-dichlorobenzene has been reported in man upon exposure to skin, manifested as eczematoid dermatitis (6).

Inhalation of 800 ppm of o-dichlorobenzene for 11 to 50 hours in rats was irritating to the eyes and nose, produced slight changes in the tubular epithelium of the kidney and caused confluent massive necrosis of the liver (11, as reported in 6). Oral administration to white rats at 0.001 mg - 0.1 mg/kg for five months caused blood dyscrasias and increased prothrombin time (14, as reported in 6). Abnormalities in conditioned reflexes were also observed. o-Dichlorobenzene increases Δ-aminolevulinic acid synthetase, the rate-limiting factor in the enzymatic synthesis of porphyrins, and in rats caused porphyria (6).

A correlation has been observed between the extent of covalent binding of halogenated benzene metabolites to protein *in vitro* and *in vivo*, and the severity of liver necrosis. Both binding and necrosis were extensive for o-dichlorobenzene in contrast to p-dichlorobenzene (6).

The Threshold Limit Value (TLV) recommended by ACGIH (1976) is 50 ppm (approximately 300 mg/m^3) (G11).

2.5 Carcinogenicity

No studies of the carcinogenicity of this compound lasting longer than 7 months could be found in the searched literature. Inhalation exposure to 49 ppm, 7 hours/day, 5 days/week of o-dichlorobenzene in the mouse and 93 ppm in the rat and guinea pig for a period of approximately 6½ months did not result in tumor formation. Oral administration of o-dichlorobenzene at 376 mg/kg to female white mice 5 days/week for approximately 6½ months did not result in tumor formation.

In another study, an unspecified isomer of dichlorobenzene gave a slight response activity in mice, in the sebaceous gland and hyperplasia tests in mice. In both cases, 0.1 ml of a 1g/100 ml solution of o-dichlorobenzene was applied 3 times to the skin of 3-4 month old, male and female Swiss mice. The sebaceous gland test was based on the disappearance of the glands after application of the compound. The hyperplasia tests involved thickening of the skin epithelium after application. On an arbitrary scale of 0 to 4 (negative to strongly positive) o-dichlorobenzene scored 0.9 on the former test and 0.7 on the latter. The significance of even strongly positive results in these tests with respect to carcinogenicity is unclear (15, as reported in 6).

Four cases of leukemia occurring in humans exposed to o or p-dichlorobenzene as solvents for other chemicals or in chlorinated benzene mixtures have been reported (G9, Vol. 7). No evidence of exposure to benzene was found. Two cases of chronic lymphoid leukemia and two cases of acute myeloblastic leukemia were reported. In the two subjects with chronic lymphoid leukemia, one had been exposed to a glue containing 2% o-dichlorobenzene from 1945-1961, and the other had been exposed from 1940-1950 to a solvent containing (80%) o-, (2%) m-, and (15%) p-dichlorobenzene, which was used for cleaning electrical parts. One of the two cases of acute myeloblastic leukemia had been exposed to the same mixture of m- and p-dichlorobenzene taken from the same factory and used for the cleaning of clothes (2 liters/year for several years); and the other case was a 15-year old girl who had "for some time" removed stains from her clothes with a product containing 37% o-dichlorobenzene (6).

2.6 Mutagenicity

A single exposure to 1-5 μl of o-dichlorobenzene did not induce reversions to histidine prototrophy in eight strains of Salmonella typhimurium in the absence of a mammalian metabolizing system (16). The metabolites of o-dichlorobenzene were not evaluated in this study. This experiment has been criticized on the grounds that a spot test is inappropriate for insoluble compounds (16) although data were presented in this study indicating that similar insoluble compounds can diffuse through agar and thus come into contact with bacteria.

A single test for mutagenicity of o-dichlorobenzene in *Aspergilus nidulans* gave inconclusive results (17).

2.7 Teratogenicity

No information can be found in searched literature for this compound. Evidence has been presented that pentachlorobenzene is teratogenic (6).

2.8 Metabolic Information

Following oral administration (0.5 mg/kg) to rabbits, o-dichlorobenzene is oxidized mainly to 3,4-dichlorophenol (40 percent). Some 3,4-dichlorophenyl mercapturic acid (5 percent) and 3,4- and 4,5-dichlorocatechol are also formed (4 percent). The phenolic metabolites are excreted mainly as o-glucuronides and sulfates in 5 to 6 days (18 as reported in 6).

Phenobarbital, an inducer of microsomal mixed-function oxidase activity, stimulated the metabolism of o-dichlorobenzene approximately 2-fold; this was blocked by SKF-525A, an inhibitor of microsomal metabolism (19).

Direct evidence for the generation of a reactive epoxide intermediate from bromobenzene suggests that a similar intermediate is formed in the metabolism of other halogenated benzenes which may be the metabolite that reacts with cellular proteins (6).

2.9 Ecological Effects

About 0.9 million lb/yr of o-dichlorobenzene are discharged to water during production. About 40 percent of the total annual production of 62.4 million lb is estimated to be for dispersive uses (G14).

The chemical was detected in 3 of 10 drinking water supplies sampled, and one that was quantified contained 1 ppb (20). The ready co-distillation of the chemical from water (Section 2.2) should diminish the amounts of this chemical in water with a corresponding increase of levels in the air.

No information on the occurrence of o-dichlorobenzene in soil and sediments, or in microorganisms and plants was found. No data on ecological effects have been found. Available data are related to experimental exposure of organisms to the chemical at levels well above those likely to occur in the environment. Some of these data follow:

o-Dichlorobenzene can cause deformities and mutagenic effects on higher plants (G14). o-Dichlorobenzene is not toxic to the microorganism Ustilago moydis (G14). It did not affect BOD at concentrations below 0.2 ppm; however, at this level the chemical inhibited the ammonification phase in saprophytic microflora (14). At 5 ppm in water in a 24-hour test, the chemical produced visible distress in trout, bluegill, and sea lamprey larvae (all 4 inches long) at 1/2, 2, and 3 hours, respectively (21). The chemical has been found in sprats and in Rhine River water (see Section 2.1).

Levels of chemical required to kill fish are exemplified by the following median lethal concentrations in the 96 hour fish bioassay, static method (22).

Bluegill (Leponis macrochirus)	27 mg/l
Tidewater silverside (Menidia beryllina)	7.3 mg/l

Although o-dichlorobenzene has not been reported in the environment, the closely related para isomer has been found in human blood and fat (see Section 2.1). The ortho isomer is likely to behave similarly and therefore has the potential of being absorbed (by inhalation) by humans.

2.10 Current Testing

o-Dichlorobenzene has been tentatively selected for testing by the NCI. Route and species are not specified (G12).

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p-DICHLOROBENZENE

2.1 Bioaccumulation

The propensity for p-dichlorobenzene to bioaccumulate is considered great. The log of the octanol/water partition coefficient is 3.38 (G15). The halogenated aromatic structure confers stability on the molecule, which helps ensure its environmental persistence and its resistance to biodegradation.

Though specific test data on the compound are not available, indications are very strong that p-dichlorobenzene will bioaccumulate. For example, blood and fat samples taken from inhabitants of the Tokyo area were found to contain the compound; fat levels were 0.2-11.7 ug/g and blood levels (on whole blood basis) 8-12 ug/ml (1). In a small model aquatic ecosystem, the following ecological magnification factors were observed for chlorobenzene with the species indicated: mosquito fish 645, mosquito larvae 1,292, snails 1,313, Daphnia 2,789, and algae 4,185. The log octanol/water partition ratio of p-dichlorobenzene (3.38) is much higher than that of chlorobenzene (2.176) (2) suggesting a greater potential for bioaccumulation. It has also been observed that p-dichlorobenzene can bioconcentrate in trout muscle. The fish to water ratio for the compound was reported to be 215 (3). Dichlorobenzene (isomer unspecified) has been identified in samples of sprat (Clupea sprattus) (4). A mixture of 7 chlorinated hydrocarbons (including o-dichlorobenzene), all known to be pollutants of Rhine water, when administered orally to rats, was found in the fat at levels 50 to 100 times that in the administered dose. Generally, highly chlorinated aromatic compounds accumulate to a greater extent than less-chlorinated aromatics (5).

2.2 Contaminants & Environmental Persistence

The technical grade liquid contains 0.08% by weight of the meta and ortho isomers. Another impurity is monochlorobenzene (G9, G14).

p-Dichlorobenzene is unreactive towards peroxide in water and ozone in air, but is very reactive to hydroxyl radical; the $t_{1/2}$ is about 3 days (G14). Products of these reactions were not given. The affinity of the compound for fatty tissues would tend to result in bioaccumulation and, therefore, increased persistence in the environment. However, only traces of the chemical have been detected in water effluents or supplies (see Section 2.9). o-Dichlorobenzene has been reported to be degraded by sewage sludge organisms (6, as reported in 9). However, this process is probably very slow since the BOD of chlorobenzene was only 0.03 g/g (7, as reported in 9) and it was noted that the introduction of chlorine atoms into an organic molecule lowered the BOD; i.e. the BOD of the dichlorobenzene should be less than the 0.03 g/g of chlorobenzene.

p-Dichlorobenzene at levels up to 300 mg/l appears to co-distill from water readily since it volatilized completely from aerated distilled water in less than four hours (8, as reported in 9). Without aeration the chemical volatilized in less than three days. Once in air, the chemical is subject to OH attack. Degradation products in water were not detected (8, as reported in 9).

2.3 Acute Toxicity

The NIOSH Registry of Toxic Effects of Chemical Substances (G16) reported the LD50 in rats for oral administration as 500 mg/kg and 2500 mg/kg for i.p. administration of commercial grade (≥ 99%) p-dichlorobenzene. The oral LD50 in mice was reported as 2950 mg/kg and 2800 mg/kg in guinea pigs. The EPA report, Investigation of Selected Potential Environmental Contaminants: Halogenated Benzenes (9) gives the LD50 for several experimental animals:

Animal	LD50 (mg/kg)	Route
mouse	3220	oral
rat	2512	oral
rabbit	2812	oral
guinea pig	7593	oral
mouse	5145	s.c.

"Moderate" exposure of humans to p-dichlorobenzene resulted in severe headaches, profuse rhinitis and periorbital swelling for approximately 24 hours after exposure. At higher concentrations, anorexia, nausea, vomiting, weight loss and yellow atrophy of the liver were reported.

Exposure of male rabbits to p-dichlorobenzene vapors (100 mg/l) for thirty minutes resulted in a range of symptoms from simple eye and nose irritation to the more usually encountered syndrome involving intense eye and nose irritation, a pronounced "marked time" reflex, muscle twitches, tremors, loss of righting reflex, definite horizontal or vertical nystagmus and rapid, labored breathing (10). Male and female Wistar rats (150-300 gm) exposed for 20 minutes to p-dichlorobenzene vapors (100 mg/l) showed affects similar to those observed in the rabbit. After each exposure there was complete narcosis with attendent tremors and twitches of the extremities. Male guinea pigs similarly exposed to p-dichlorobenzene exhibited the same symptoms as rabbits and rats, the symptoms lasting for 1-1½ hours (10).

2.4 Other Toxic Effects

Exposure of male workers who manufactured p-dichlorobenzene for 1 - 7 months resulted in loss of weight, exhaustion, decrease of appetite and blood dyscrasia (11, as reported in 9). Exposure to p-dichlorobenzene in mothball vapor in two humans for 3 - 4 months is reported to have resulted in weight loss, loose bowels, tarry stools, numbness, abdominal swelling, jaundice and clumsiness (12, as reported in 9).

Inhalation of 0.95-2.05 mg/l of p-dichlorobenzene for 7 hour/day, 5 days/week for 16 days in male and female rats, guinea pigs and rabbits had no adverse effects on growth or survival. Increases in the weight of liver, kidneys and spleen were noted. Cloudy and granular swelling of the liver was observed in exposed rats. No adverse effects were observed upon exposure of experimental animals to 0.58 mg/l of p-dichlorobenzene (13).

In another study rabbits exposed to 4.6-4.8 mg/l of p-dichlorobenzene for 8 hours/day exhibited muscular weakness, tremors, nystagmus, edema of the cornea and transitory edema of the optic nerve. Some animals died after a few days while a few withstood 62 days exposure (14, as reported in 9). Rats subjected similarly to toxic concentrations of p-dichlorobenzene (100 mg/l) for 5-9 days exhibited a greater degree of CNS depression and increased irritation of mucosa. Granulocytopenia was also present (10).

Oral administration of p-dichlorobenzene (500 mg/kg) to adult male rats, 5 days/week for 4 weeks, resulted in marked cloudy swelling and necrosis in the central area of the liver lobules and marked cloudy swelling of the renal tubular epithelium with cast formation. No adverse effects were observed after 10-100 mg/kg dosages (15).

Oral administration of 376 mg/kg of p-dichlorobenzene to female rats 5 days/week for 27 weeks produced an increase in liver, spleen, and kidney weight, slight cirrhosis and focal necrosis of the liver. At 188 mg/kg an increase in liver and kidney weight was observed No adverse effects were observed at 18.8 mg/kg of p-dichlorobenzene (15).

Rabbits fed a 25% solution of p-dichlorobenzene in olive oil at 500-1000 mg/kg, 5 days/week for 7-8 months, exhibited weight loss, tremors, weakness and slight changes in the liver characterized by cloudy swelling and a very few areas of focal caseous necrosis (15).

No increase Δ-aminolevulinic acid synthetase, the rate-limiting factor in the enzymatic synthesis of porphyrins, was observed in rats given p-dichlorobenzene (250 mg/kg p.o.) for three days, although porphyria was produced upon administration of 770 mg/kg of this compound for five days. Slight increases in hepatic glucuronyl transferase and azoreductase activity and EPN detoxification were observed following p.o. administration of p-dichlorobenzene (40 mg/kg) (22, as reported in 9).

A correlation has been observed between the extent of covalent binding of halogenated benzene metabolites to protein *in vitro* and *in vivo*, and the severity of liver necrosis. In contrast to o-dichlorobenzene, protein binding and liver necrosis was low for the *para*-isomer (21).

Intramuscular injection of guinea pigs with p-dichlorobenzene (125-250 mg/kg) for 10-12 days resulted in weight loss, intense steatosis of the liver, decreased liver glycogen and increased blood serum transaminase (16, as reported in 9).

The Threshold Limit Value (TLV)® recommended by the ACGIH (1976) is 75 ppm (approximately 450 mg/m^3) (G11).

2.5 Carcinogenicity

No studies of the carcinogenicity of this compound involving exposures longer than 7 months could be found in the searched literature.

The EPA report (9) cites carcinogenicity studies on p-dichlorobenzene by Hollingsworth *et al*. (1956), although the original paper does not give any information about carcinogenicity.

No tumors were observed in inhalation experiments with guinea pigs, rabbits, mice and monkeys at 96-798 ppm p-dichlorobenzene, administered 8 hours/day, 5 days/week for 6-7 months. No tumors were observed in rats given (18.8-376 mg/kg) p-dichlorobenzene via stomach tube, 5 days/week for 6-7 months (15, as reported in 9).

In another study 10 mice received 9 doses of p-dichlorobenzene (0.4 mg/injection) subcutaneously at varying intervals over a period of two months. Four mice died within a month. By the 77th day, one out of six remaining mice exhibited a sarcoma with secondary growths in the lymph glands and peritoneum (17). Because of the small number of animals and short observation period it is difficult to determine the significance of this observation.

2.6 Mutagenicity

Exposure of Aspergillus nidulans (meth$_3$-) to 200 ug/ml of p-dichlorobenzene for sixty minutes was reported to induce an increase in the frequency of reversion to methionine prototrophy from 3 to 11 out of 10^6 spores. The increase in reversion was significantly greater than that observed for o-dichlorobenzene. Since only one dose was tested, the data are not fully conclusive evidence of mutagenicity (18).

2.7 Teratogenicity

No information has been found in the searched literature for this compound, although evidence has been presented that pentachlorobenzene is teratogenic (19, as reported in 9).

2.8 Metabolic Information

p-Dichlorobenzene administered orally to rabbits (0.5 mg/kg) is oxidized mainly to 3,4-dichlorophenol (35%). No mercapturic acid or catechols were detected although quinol was found. The phenolic metabolite is mainly excreted as glucuronide and sulfate conjugates in 5-6 days (20, as reported in 9).

Phenobarbital, an inducer of microsomal mixed-function oxidase activity, stimulated the rate of metabolism of p-dichlorobenzene, while SKF-525A, an inhibitor of microsomal metabolism, decreased the oxidation of this compound (21). p-Dichlorobenzene increased the urinary excretion of porphyrin and its precursors in the male rats given this compound (770 mg/kg) for five days.

Fish, amphibians, and insects possess enzyme-systems that are capable of metabolizing halogenated benzenes. Trace amounts of 2,5-dichlorophenol were detected in the frog, *Rana pipiens*, after administration of p-dichlorobenzene (23, as reported in 9).

2.9 Ecological Effects

About 1.2 million lb/yr of the chemical are discharged to water during production. About 90 percent of the total annually produced 77.3 million lb is estimated to be for dispersive uses (G14).

The widespread use of the chemical in the home and city (as a space odorant and in moth control (G14) appears to be largely responsible for the finding of p-dichlorobenzene in the blood (8-12 μg/ml) and fat (0.2-11.7 μg/g) of Tokyo residents (8) (See Section 2.1). It appears that persons using household products containing the chemical may be exposed via inhalation to high concentrations of the chemical. Some reported concentrations (μg/ m^3) of the chemical in the home were: inside wardrobe 1700, inside closet 315, bedroom 105 (1). Concentrations in the ambient air of central Tokyo were 2.7-4.2, in suburban Tokyo 1.5-2.4 (1). Effects of this exposure, however, have not been reported.

Traces of the chemical have been detected in 4 of 10 drinking water supplies sampled, and one that was quantified contained 0.5 ppb (24). The ready co-distillation of the chemical from water (section 2.2) should diminish the levels of this chemical in water with a corresponding increase of levels in the air.

No information on the occurrence of the chemical in soil and sediments, or in microorganisms and plants was found in the searched literature.

No data on ecological effects were found. The data that have been reported are related to experimental exposure of organisms to the chemical, and these are at levels above those in the environment. Some of these data follow:

> Dichlorobenzene can cause deformities and mutagenic effects on higher plants (G14). The chemical is not toxic to the microorganism Ustilago maydis (G14). It did not affect BOD at concentrations below 0.2 ppm; however, at this level the chemical inhibited the ammonification phase in saprophytic microflora (11). Narcotic effects were observed within 6 minutes after frogs and toads were exposed to vapors of the chemical (15). Three of 10 ducks died after 28 days on a diet containing 0.5% of the chemical; the remaining ducks survived the 35-day subacute oral toxicity test (15).

2.10 Current Testing

p-Dichlorobenzene has been tentatively selected for testing by the NCI. Route and species are not specified. Testing is currently in progress by N. Ito at Nagoya City University Medical School, Nagoya, Japan in mice p.o. in diet (G13).

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CHLORINATED PARAFFINS, 35-64% CHLORINE

TABLE OF CONTENTS

Page

Overview IV-1

Part I - General Information IV-3

Part II - Biological Properties

- 2.1 Bioaccumulation IV-8
- 2.2 Contaminants and Environmental Degradation or Conversion Products IV-9
- 2.3 Acute Toxicity IV-10
- 2.4 Other Toxic Effects IV-11
- 2.5 Carcinogenicity IV-11
- 2.6 Mutagenicity IV-11
- 2.7 Teratogenicity IV-11
- 2.8 Metabolic Information IV-11
- 2.9 Ecological Effects IV-11
- 2.10 Current Testing IV-12
- References IV-13

CHLORINATED PARAFFINS 35-64% CHLORINE

AN OVERVIEW

Chlorinated paraffins (CP) are commercial products which are prepared by chlorination of paraffin oils and paraffin waxes. These products are mixtures of related compounds and are expected to vary depending on feedstocks and manufacturing conditions. In 1976, U.S. production of chlorinated paraffins in the 35-64% chlorine range was 60.2 million lbs.

These compounds are industrially used as high pressure lubricants, flame retardants and plasticizers. They have numerous consumer uses in paints, varnishes, flame retardants and household aerosols among other products.

It is estimated that 50.3 million pounds of 35-64% chlorinated paraffins are annually released into the environment, and that approximately 1.75 million workers are occupationally exposed to the wax annually.

It has been shown in Rainbow trout that the higher the molecular weight of the chlorinated paraffin mixture the higher the bioaccumulation in fish tissue. When juvenile Atlantic salmon were fed with certain chlorinated paraffins a high mortality rate was observed. Otherwise, little information could be found in the literature searched on the environmental effects or stability of these chemicals.

Chlorinated paraffins have been generally considered as relatively non-toxic. However, fatty degeneration of the liver and changes in the spleen in rats following ingestion of these compounds have been reported in a Russian article. In addition, toxic contaminants may be present in commercial paraffin products. No information on their carcinogenicity, mutagenicity and teratogenicity was found in the searched literature.

CHLORINATED PARAFFINS, 35-64% CHLORINE

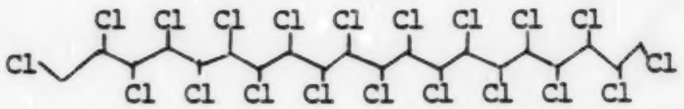
PART I

GENERAL INFORMATION

1.1 Identification

All chlorinated paraffin (CP) products are mixtures of isomers and congeners of chlorinated hydrocarbons. The particular structures and their proportions in a CP mixture depend on three factors: the nature of the paraffin mixture used as raw material; the extent of chlorination and the method of chlorination. The principal raw materials employed in the manufacture of CPs are paraffins, which are petroleum fractions consisting mainly of straight-chain hydrocarbons. Certain CP products, derived from paraffins of average molecular weight about 150, are liquids. CP products which are derived from paraffins, of average molecular weight 320, are hard, waxy solids. A purified petroleum fraction, consisting predominantly of eicosane ($C_{20}H_{42}$) has been used as a raw material (G17).

Paraffins can be chlorinated to a maximum of about 70% chlorine by weight, which corresponds to about one chlorine atom per carbon of the paraffin chain (G17). Useful properties are found in the 35-70% chlorine range. Table 1 lists several commercial chlorinated paraffin mixtures, their starting materials, average molecular formula and chlorine content. A representative chlorinated paraffin component, chlorinated eicosane, is shown below.



Estimates of the number of components in CP mixtures were not found in the searched literature.

Table 1. Average Compositions of Typical Commercial Chlorinated Paraffins (adapted from G17)

			Commercial Paraffins					
Raw material	Chlorine content, %	Av mol formula	Diamond Alkali Co.	Hercules Powder Co.	Farbwerke Höchst	Chemische Werke Hüls	Imperial Chemical Industries	Chemische Werke Witten
paraffin wax	40	$C_{23}H_{42}Cl_6$	Chlorowax 40	Chlorafin 42	Chlorparaffin 40		Cereclor 42	
paraffin wax	40	$C_{20}H_{37}Cl_5$	Chlorowax LV					
paraffin	40	$C_{14}H_{26}Cl_4$				Chlorparaffin 40		
paraffin wax	48-54	$C_{23}H_{40}Cl_8$					Cereclor 48	
paraffin wax	48-54	$C_{20}H_{34}Cl_8$	Chlorowax 50				Cereclor 54	
paraffin wax	48-54	$C_{14}H_{24}Cl_6$			Chlorparaffin 50	Chlorparaffin 52	Cereclor P 50	Chlorparaffin K 53
paraffin	60-65	$C_{11}H_{17}Cl_7$			Chlorparaffin 64	Chlorparaffin 60		

1.2 Synonyms and Trade Names

Paraffin, chlorinated; chlorcosane; cereclor; chlorowax; chlorez; see also Table 1

1.3 Chemical and Physical Properties

1.3.1 Description:

Depending on the chain length and chlorine content, chlorinated paraffins range from oily liquids to viscous liquids to waxy solids. The mixtures are tasteless, odorless and nonflammable. (G2)

1.3.2 Melting Point:

The solid product of 70% chlorine content prepared from a paraffin wax of average molecular weight 320 has a melting range of 85-90°C. (G17)

1.3.3 Vapor Pressure:

For several products the vapor pressures are reported as less than 10^{-4} mm H_g at 65°C. (G17)

1.3.4 Solubility:

Insoluble in water and lower alcohols; soluble in chlorinated and aromatic organic solvents. Also soluble in common oils and plasticizers. (G17)

1.4 Production and Use

1.4.1 Production:

48.8 Million lbs (1972)
57.545 Million lbs (1975)
60.210 Million lbs (1976) (G24)

1.4.2 Use:

Used in high pressure lubricants; as flame retardant in plastics and textiles; as plasticizer for polyvinyl chloride in polyethylene sealants; detergents; food packaging. (2, G21)

CONSUMER PRODUCT INFORMATION

Category	Number of Products Containing Chlorinated Paraffins	Percentage of Products in Category Containing Chlorinated Paraffins
Chlorinated paraffin wax		
Paints, varnishes, shellac, rust preventatives, etc.	33	0.3%
Flame retardant chemicals	31	5.2%
Household aerosols	1	0.03%
65 products surveyed averaged 22.1% chlorinated paraffin wax		
Chlorinated paraffin		
Paints, varnishes, shellac, rust preventatives, etc.	15	0.1%
Flame retardant chemicals	4	0.6%
Household aerosols	1	0.03%
Adhesives and adhesive products, incl. glue	1	0.2%
21 products surveyed averaged 5.7% chlorinated paraffin		
Chlorowax 40		
Paints, varnishes, shellac, rust preventatives, etc.	19	0.2%
Flame retardant chemicals	1	0.2%
Household aerosols	1	0.03%
21 products surveyed averaged 2.3% chlorowax 40		
Chlorinated n-paraffins		
Flame retardant chemicals	13	2.2% (G27)
13 products surveyed averaged 92.6% chlorinated n-paraffins		

1.5 Exposure Estimates

1.5.1 Release Rate:

50.3 Million lbs. (G28)

1.5.2 NOHS Occupational Exposure:

Rank: Chlorinated paraffin wax: 66

Estimated number of persons exposed: 1,757,000 (G29)

1.6 Manufacturers

Ferro Corp.
Hercules, Inc.
ICC Industrial, Inc.
ICI United States, Inc.
Neville Chemical Co.
Pearsall Chemical Corp.
Plastifax, Inc.
Riverside Chemical Co.

CHLORINATED PARAFFINS, 35-64% CHLORINE

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

Rainbow trout were fed a CP product mixed into the diet for 82 days (1). The diet contained 10 ppm of "Chlorowax 500C", a 50% chlorine product. Tissue residues were determined by gas chromatography.

CP residues steadily increased throughout the experiment to a maximum of 1.1 ppm at 82 days. The authors noted differences in the gas chromatographic elution pattern of the tissue residues as compared to the starting mixture. The higher molecular weight components of the chlorinated paraffin mixture were more residual in fish tissue. This was shown by a shift toward later-eluting CP components in the fish as the experiment progressed.

Uptake of two chlorinated paraffin mixtures by juvenile Atlantic salmon has been studied (2). The two CP products were of 42 and 70% chlorine content. Each was administered in two ways: adsorbed on silica and mixed in food. Two fish were exposed to CP-coated silica particles and 10 fish were fed CP-containing food. Fish CP residues were determined as total chlorine, and were expressed in ppm total chlorine (based on wet weight). In the silica experiments, two fish (combined weight 5-7 g) were exposed to a total of 2 mg of chlorinated paraffin adsorbed on 2 g of silica in 2 liters of water. After 48 hours of exposure, the fish had body residues of 0.44 and 0.22 μg/g from the 42 and 70% chlorine products, respectively. After 144 hours the corresponding tissue residues were 0.75 and 0.46 ppm. In this experiment the control fish had 0.34 μg/g of chlorine of an unspecified nature.

In the fish feeding trials, experimental levels of 10 and 100 ppm of the two chlorinated paraffins were fed in the diet of juvenile salmon for 33, 109 and 181 days. After 33 days the fish fed the 42% product had body residues of 0.11 and 0.51 ppm at the respective feeding levels of 10 and 100 ppm. In the 70% chlorinated paraffin group, tissue residues were 0.29 and 0.49 ppm after 33 days. The control group had a chlorine residue of 0.3 ppm at this time. At later sampling times none of the tested groups, including the controls, had any detectable chlorinated residue.

2.2 Contaminants and Environmental Degradation or Conversion Products

The definition of what is a contaminant in a product which is a mixture of many components is not clear. If chlorinated paraffins are taken to mean mixtures of partially chlorinated straight-chain alkanes, then any branched-chain isomers or alicyclic or aromatic impurities will be contaminants. Such materials may be present from the petroleum-derived raw materials used in the production of chlorinated paraffins, but no confirmation or denial of these possibilities has been found in the searched literature. Reported contaminants of chlorinated paraffin mixtures include carbon tetrachloride (G17), chlorine (G14), hydrogen chloride (G14), epoxy compounds (G14), various metals (G14) and stabilizers such as glycols, phosphates or derivatives of tin, lead and cadmium (G17). These stabilizers are added to the commercial products to inhibit thermal dehydrochlorination.

Under non-biological conditions, the chlorinated paraffins are quite stable. At temperatures above 100°C or in the presence of strong bases they will lose hydrogen chloride to give chlorinated olefins. They have very low volatility and negligible water solubility. Upon application to water it is expected that chlorinated paraffins will be adsorbed onto the sediment.

Bacteria are reported to degrade chlorinated paraffins (G14), but the degradation products are not known.

2.3 Acute Toxicity

Oral LD50 values of 21 and 26 g/kg have been reported for the mouse and the rat, respectively (3). There is no evidence that these products are associated with skin irritation or sensitization. Eye irritation in animals has been noted (3).

2.4 Other Toxic Effects

No information on other toxic effects was found in primary sources. A secondary source (G14) reported a Russian article claiming that repeated dosing ($<$ 1 year, inhalation) in the mouse produced fatty degeneration of the liver and various generative (*sic*) changes in the spleen. No information on dosage is available.

2.5 Carcinogenicity

No information found in searched literature.

2.6 Mutagenicity

No information found in searched literature.

2.7 Teratogenicity

No information found in searched literature.

2.8 Metabolic Information

No information found in searched literature.

2.9 Ecological Effects

In a long term feeding study (up to 181 days) juvenile Atlantic salmon suffered higher mortality than controls when fed diets containing "Cereclor 42" and "Chlorez 700" at 10 and

100 ppm in the diet as shown below (2). No explanation is given for the reverse dose response in the Cereclor 42 data.

LT50 of juvenile Atlantic salmon in the feeding experiment

Feeding		LT50 (days)
Control		138
Cereclor 42,	10 μg/g	47
	100 μg/g	80
Chlorez 700,	10 μg/g	71
	100 μg/g	39

No gross toxicological effects were noted in fingerling rainbow trout when fed a diet fortified with 10 ppm "Chlorowax 500C" for up to 82 days, although their weight gain was significantly less than that of the controls (1).

2.10 Current Testing

Chlorowax 40 and Chlorowax 500C, 35-64% chlorinated paraffins, have been tentatively selected for carcinogenesis bioassay study by National Cancer Institute (approved in September 1977) (G12).

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CHLOROMETHANE

TABLE OF CONTENTS

Page

Overview V-1

Part I - General Information V-3

Specific References V-5

Part II - Biological Properties

2.1 Bioaccumulation V-6

2.2 Contaminants and Environmental Degradation or Conversion Products V-6

2.3 Acute Toxicity V-7

2.4 Other Toxic Effects V-8

2.5 Carcinogenicity V-9

2.6 Mutagenicity V-9

2.7 Teratogenicity V-9

2.8 Metabolic Information V-9

2.9 Ecological Effects V-10

References V-12

CHLOROMETHANE

AN OVERVIEW

Chloromethane (or methyl chloride) is a colorless gas at room temperature and pressure. It has a slight odor that is not sufficiently characteristic or unpleasant to warn of exposure to dangerous concentrations. It is soluble in water, alcohol, ether, acetone, benzene, chloroform and acetic acid.

Production of chloromethane in the U.S. is primarily by reaction of hydrogen chloride with methanol. In several plants the chloromethane is further reacted with chlorine to produce methylene chloride, chloroform, or carbon tetrachloride. In 1976, the production of chloromethane totaled 377 million pounds. From 1965-1975 production increased by 5.3% per year. The Chemical Marketing Reporter (March 29, 1976) projected an annual rise in production of 6% through 1980.

Chloromethane is used primarily as an industrial intermediate in the production of silicones and tetramethyllead. Additional minor uses are as a catalyst solvent in butyl rubber manufacture, in the production of methyl cellulose, as a propellant in high pressure aerosols and as an anesthetic. In the past, it has been used extensively as a refrigerant.

It is estimated that currently about 5% of the annual production (over 18 million pounds per year) is released into the environment. According to NIOSH, about 31,000 workers are exposed to chloromethane.

Chloromethane is reported to be a natural product, formed in the oceans and by combustion of vegetation (e.g., argicultural burning and forest fires). Combustion of polyvinyl chloride in waste is believed to be a larger source of release to the environment than losses of the industrially synthesized product. It is widespread in the atmosphere and may play a minor role in the destruction of stratospheric ozone.

Exposure to chloromethane has been implicated in damage to the central nervous system, liver, kidneys, and lungs. Chloromethane exhibits mutagenic properties in the *Salmonella* reversion test without microsomal enzyme activation. No reports on carcinogenicity, teratogenicity and chonic toxicity were found.

CHLOROMETHANE

PART I

GENERAL INFORMATION

1.1 **Identification** CAS No.: 000074873
NIOSH No.: PA63000
(G16)

1.2 Synonyms

Methyl chloride (G22)

1.3 Chemical Formula and Molecular Weight

CH_3Cl Mol. wt. 50.49 (G22)

1.4 Chemical and Physical Properties

1.4.1 **Description:** Colorless gas; compresses to a colorless liquid of ethereal odor and sweet taste (G23)

1.4.2 **Boiling Point:** -24.2° C (G22)

1.4.3 **Melting Point:** -97.73° C (G22)

1.4.4 **Absorption Spectrometry:**

No information found in sources searched

1.4.5 **Vapor Pressure:** 5 atm at 22° C (G22)

1.4.6 **Solubility:** Soluble in water and alcohol; Soluble in all proportions in ether, acetone, benzene, chloroform and acetic acid (G22)

1.4.7 **Octanol/Water Partition Coefficient:**

$\log P_{oct} = 1.08$ (estimate) (G36)

1.5 Production and Use

1.5.1 **Production:**
453.500 Million lbs (1972)
366.449 Million lbs (1975)
377.672 Million lbs (1976) (G24)

1.5.2 **Use:** As a catalyst carrier in low-temperature polymerization (butyl rubber); in manufacturing of tetramethyllead, silicones; as a refrigerant; as an anesthetic in medicine; as a fluid for thermometric and thermostatic equipment; as a methylating agent in organic synthesis such as methylcellulose; as an extractant and low-temperature solvent; as a propellant in high-pressure aerosols; as a herbicide (G21,G23)

Quantitative Distribution:

	Percent
Silicones	40
Tetramethyllead	35
Butyl rubber	4
Methyl cellulose	4
Herbicides	4
Quaternary amines	4
Miscellaneous	9
	100

(1)

1.6 Exposure Estimates

1.6.1 Release Rate:

18.1 Million lbs (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 1814

Estimated no. of persons exposed: 31,000*

*rough estimate

(G29)

1.7 Manufacturers

Allied Chemical Corp.
Continental Oil Co.
Diamond Shamrock Corp.
Dow Chemical, USA
Dow Corning Corp.
E.I. du Pont de Nemours and Co.
Ethyl Corp.
General Electric Co.
Stauffer Chemical Co.
Union Carbide Corp.
Vulcan Materials Co. (G25)

Specific Reference for Part I

1. Chemical Profile, Methyl Chloride, Chemical Marketing Reporter, March 29, 1976 .

CHLOROMETHANE

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

No report on the bioaccumulation of chloromethane could be found in the searched literature. The high vapor pressure (5 atm. at 22° C) and significant water solubility (ca. 0.7%, 303 ml gas/100 g water, 20° C (G23)) indicate that chloromethane has a low potential for bioaccumulation.

2.2 Contaminants and Environmental Degradation or Conversion Products

Since chloromethane is nearly odorless, acrolein has sometimes been added to serve as a warning agent (G3). When manufactured by direct chlorination (2% of current U.S. production), chloromethane is also likely to be contaminated with, in decreasing order of quantity, dichloro-, trichloro-, and tetrachloromethanes. Most chloromethane is made by hydrochlorination of methanol. The most likely contaminants in the product are water vapor and hydrogen chloride gas (7).

Though it is thermally stable up to 800° F (427° C), when heated to decomposition it emits highly toxic fumes of hydrogen chloride and other toxic gases (G5). Chloromethane is stable when dry but in contact with moisture undergoes slow decomposition to hydrochloric acid and methanol (G4).

2.3 Acute Toxicity

The NIOSH Registry of Toxic Effects of Chemical Substances (G16) reports the lowest lethal concentrations of chloromethane as follows:

Parameter	Dosage	Animal	Route
LCLo	3,146 ppm/7H	mouse	inhalation
LCLo	20,000 ppm/2H	guinea pig	inhalation

The following effects have been reported in guinea pigs and other unspecified animals after acute inhalation exposures: death in a short time at 150,000-300,000 ppm; serious effects in 30-60 minutes at 20,000-40,000 ppm; no serious effects for up to 60 minutes at 7,000 ppm; no effect for up to 8 hours at 500-1000 ppm (1). Narcosis occurs at 40,000 ppm in rabbits and at 108,600 ppm in cats (2).

Human poisonings resulting from the use of chloromethane as a refrigerant have been reported fairly frequently in the past. Over 200 cases have been reported prior to 1961, involving some 20 deaths (3). An important factor in many poisoning incidents is that the gas is colorless and almost odorless and produces no perceptible irritation to the eyes, so that the victim is often unaware of its presence even at toxic levels.

The concentrations required to produce toxic effects in man have not been established precisely. Von Oettingen (2) and Scharnweber *et al*. (4) state that most cases of intoxication by chloromethane have involved concentrations well above 500 ppm.

Symptoms following acute exposures include drowsiness, dizziness, misty vision, mental confusion, staggering gait, and slurred speech. In more severe cases, symptoms include ataxia, double vision, nausea, vomiting, general muscular spasms, diarrhea, and sometimes convulsions with cyanosis and unconsciousness (2,4). The primary cause of death appears to be cerebral and pulmonary edema associated with circulatory failure (2).

Pathological findings in fatal poisonings with chloromethane include congestion, edema, and hemorrhages in various organs, particularly in the lungs; fatty changes in the liver; and degeneration of the kidneys. There may be focal changes in the central nervous system, spinal roots, and ganglia in certain sections of the brain (2). Acute hemolysis has also been reported in addition to damage to the kidney and liver (3).

2.4 Other Toxic Effects

Chloromethane acts as a central nervous system depressant in humans. Light cases of intoxication are marked by a characteristic latent period of one half to several hours between exposure and the onset of symptoms. Recovery usually occurs within 5-6 hours. In more severe cases damage to the kidney and liver may occur, but neurological symptoms are usually more prominent. Some central nervous system effects may be long-lasting and post-recovery symptoms such as headache, insomnia, and nervousness may persist (2,4).

Chloromethane also produces neurological disturbances in several animal species at concentrations lower than those required to produce narcosis (2). Concentrations of 15,000 and 40,000 ppm produced a primary increase in the heart rate and a rise in arterial and venous blood pressure in dogs (2).

The Threshold Limit Value (TLV) for chloromethane has been set by the ACGIH at 100 ppm (approximately 210 mg/m^3) (G11).

No long-term toxicological studies have been found in the literature searched.

2.5 Carcinogenicity

No data on the carcinogenicity of chloromethane were found in the searched literature.

2.6 Mutagenicity

Chloromethane has been reported to be mutagenic in the *Salmonella typhimurium* tester strain TA 1535 (5). No significant difference between the number of revertant colonies with or without added rat liver homogenate was observed, indicating that metabolic activation is not required to promote mutagenesis. In another report, chloromethane was found to be mutagenic in *S. typhimurium* strain TA 100 (base-pair substitutions with overlap to frameshift mutations)(6).

2.7 Teratogenicity

No information on the teratogenicity of this compound was found in the searched literature.

2.8 Metabolic Information

Chloromethane is broken down in the body into methanol and hydrochloric acid. The neutralization of the acid forms chlorides, which have no toxicological importance. The speed and extent of the preliminary breakdown of chloromethane in the body are not known. However, the excretion of chloromethane is very slow and occurs mainly through the lungs (G3). Redford-Ellis and Gowenlock (8) report that death from chloromethane intoxication may be the result of the accumulation of methylglyoxal in the brain. Methylglyoxal is normally converted to lactic acid, but this process is impaired by the presence of monohalomethanes (8). Davis et al. (7) and Flury (cited in ref. 2) have suggested that the toxic effects of chloromethane may be attributable to its hydrolysis to methanol and subsequent oxidation to formaldehyde.

2.9 Ecological Effects

There is a considerable amount of information (9,10,11) that indicates that chloromethane is a natural environmental constituent. It has been suggested (9) that a major source of chloromethane may be microbial fermentation (12) and smoldering and combustion of vegetation. It has been estimated (9) that 1% of the chlorine content of vegetable matter is converted to chloromethane. Palmer (13) has estimated the total amount of chloromethane produced by combustion in the United States as 2×10^5 metric tons per year, considerably larger than the estimated rate of release of the synthesized product. Forty percent of the total was estimated to be produced in burning buildings and by burning polyvinyl chloride in waste, with the rest stemming from agricultural burning and forest fires (13).

Chloromethane is also present in cigarette smoke (about 0.6 mg per cigarette (14,15)).

The oceans are probably a major source of chloromethane(9, 11). The presence of chloromethane in drinking water has been reported, possibly formed during the process of chlorination (6,7). Chloromethane is also detected as a result of the use of bromoethane as a fumigant on stored wheat (7). Davis *et al*. (7) suggest the probability that the amount of chloromethane formed may be related to the chlorine content of the food.

Chloromethane is widely distributed in the atmosphere, typically at concentrations of the order of one part per billion (9,10,11). Although it is removed from the troposphere by various processes, small quantities diffuse upward into the stratosphere and are believed to play a role in the catalytic destruction of ozone (16,17). However, the importance of anthropogenic chloromethane in stratospheric ozone depletion is believed to be small relative to that of other synthetic halocarbons (16,17).

The Aquatic Toxicity Rating (96 hr TLm, species unspecified) of chloromethane is stated to be over 1000 ppm (G16).

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CRESOLS

TABLE OF CONTENTS

Page

Overview VI-1

Part I - General Information

Cresol (mixed isomers) VI-3

m-Cresol VI-6

o-Cresol VI-8

p-Cresol VI-10

Summary of Characteristics VI-12

Part II - Biological Properties

2.1 Bioaccumulation VI-13

2.2 Contaminants and Environmental Degradation or Conversion Products VI-13

2.3 Acute Toxicity VI-14

2.4 Other Toxic Effects VI-15

2.5 Carcinogenicity VI-16

2.6 Mutagenicity VI-17

2.7 Teratogenicity VI-17

2.8 Metabolic Information VI-17

2.9 Ecological Effects VI-18

2.10 Current Testing VI-18

References VI-19

CRESOLS

AN OVERVIEW

There are three isomers of cresol: o-cresol, m-cresol, and p-cresol. All three isomers as well as mixtures are articles of commerce. Cresols are solid or liquid at room temperature (melting points 11-35°C). They are slightly soluble in water and soluble in organic solvents.

The composition of the commercial products depends on the method of production and upon the degree of refining. Cresols are sold in a wide variety of grades, varying in composition, color, and boiling range. Technical grade cresols commonly contain xylenols and phenol. A less refined product called creosote oil contains 10-20% by volume of tar from the coking process. Total annual production of cresols in the United States is probably in excess of 100 million pounds.

Cresols are used for a wide variety of purposes: disinfectants, solvents, in ore flotation, and as intermediates in the production of phosphate esters and phenolic resins. They are also present in a number of consumer products, including disinfectants, metal cleaners, and motor oil additives.

The number of persons occupationally exposed to cresols is estimated to be two million. Environmental release of the mixed isomers and of the p- and o-isomers are estimated at 30 million pounds and 16 million pounds, respectively.

Cresols have a broad spectrum of toxicity to micro-organisms and are used as disinfectants and fungicides. There is little other information on their potential toxicity to wildlife. Cresols are relatively easily metabolized by mammals and microorganisms and are unlikely to undergo significant bioaccumulation.

Cresols are moderately toxic to mammals by ingestion and dermal exposure, and are corrosive to skin and other tissues. Little information is available on effects of chronic exposure. In one experiment all three isomers of cresol were reported to promote the carcinogenicity of dimethylbenzanthracene on mouse skin. _m_-Cresol caused developmental abnormalities in toad embryos. Otherwise, no significant information is available on the potential carcinogenicity, mutagenicity, or teratogenicity of cresols.

CRESOLS

PART I

GENERAL INFORMATION

I. Cresol (mixed isomers)

1.1 Identification

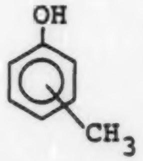
CAS No. 001319773
NIOSH No. GO59500

1.2 Synonyms and Trade Names

Cresylic acid; methyl phenol; hydroxytoluene; tricresol; cresylol

(G23,G21, G16)

1.3 Chemical Formula and Molecular Weight



C_7H_8O Mol. Wt. 108.15

(G23)

1.4 Chemical and Physical Properties

1.4.1 **Description:** A mixture of isomers in which m-isomer predominates, obtained from coal tar or petroleum; colorless, yellow or pinkish liquid; phenolic odor; combustible; becomes darker with age and on exposure to light.

(G21,G23)

1.4.2 **Boiling Point:** 191 - 203° C (G21)

1.4.3 **Melting Point:** 11 - 35° C (G21)

1.4.4 **Absorption Spectrometry:**

No information found in sources searched

1.4.5 **Vapor Pressure:** No information found in sources searched

1.4.6 **Solubility:** Soluble in alcohol, glycol, dilute alkalis, ether, chloroform;
Slightly soluble in water

(G21,G25)

1.4.7 **Octanol/Water Partition Coefficient:**

$\text{Log } P_{oct} = 2.70$ (estimate)

1.5 Production and Use

1.5.1 Production:

~60	Million lbs	(1968)
~80	Million lbs	(1973)

(G25)

1.5.2 Use:

As a disinfectant; intermediate in manufacturing of phenolic resins, tricresyl phosphate, salicylaldehyde, coumarin, and herbicides; as an ore flotation agent; as a textile scouring agent; as an organic intermediate; as a surfactant

(G21)

Quantitative Distribution of Uses:

	Percent
Phosphate esters	22
Magnet wire	15
Antioxidants	15
Resins	15
Exports	10
Cleaning and disinfectant compounds	6
Ore flotation	6
Miscellaneous	11
	100

(G25)

Consumer Product Information:

Cresol is present in:

automotive parts cleaner
metal cleaner, stripper, degreaser
disinfectant
motor oil additive
carbon remover
embalming supplies

(G35)

1.6 Exposure Estimates

1.6.1 Release Rate: 30.4 Million lbs (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 105

Estimates no. of persons exposed: 1,914,000

(G29)

1.7 Manufacturers

American Cyanamid Co.
Amoco Oil Co.
Crowley Tar Products Co., Inc.
Freese Chemicals,
Koppers Co., Inc.
Merichem Co.,
Mobil Oil Corp.
Northwest Petrochemical Corp.
Pitt-Consol Chemicals
Productol Chemical Co.
Sherwin-Williams Co.
United States Steel Corp.

(G25)

CRESOLS

II. *m*-Cresol

1.1 Identification

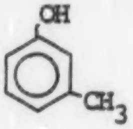
CAS No.: 000108394
NIOSH No.: GO61250

1.2 Synonyms and Trade Names

m-Cresylic acid; *m*-methylphenol; 3-methylphenol; 1-hydroxy-3-methylbenzene; *m*-kresol; *m*-oxytoluene

(G16)

1.3 Chemical Formula and Molecular Weight



C_7H_8O Mol. wt. 108.15

(G22)

1.4 Chemical and Physical Properties

1.4.1 **Description:** Colorless to yellowish liquid; phenol-like odor (G21)

1.4.2 **Boiling Point:** 202.2° C (G22)

1.4.3 **Melting Point:** 11.5° C (G22)

1.4.4 **Absorption Spectrometry:**

$$\lambda_{max}^{hexane} = 214, 271, 277$$

$$\log \epsilon = 3.79, 3.20, 3.27$$ (G22)

1.4.5 **Vapor Pressure:** 1 mm at 52.0° C (G22)

1.4.6 **Solubility:** Slightly soluble in water;
Soluble in hot water, organic solvents;
Soluble in all proportions in alcohol, ether, acetone, benzene and carbon tetrachloride

(G22)

1.4.7 **Octanol/Water Partition Coefficient:**

$$\log P_{oct} = 2.37$$ (G15)

1.5 Production and Use

1.5.1 Production:

No information found in sources searched

1.5.2 **Use:** In disinfectants and fumigants; in photographic developers, explosives (G23)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure:

Rank: 2781

Estimated no. of persons exposed: 9,000*

*rough estimate (G29)

1.7 Manufacturers

Koppers Co., Inc. (G24)

CRESOLS

III. *o*-Cresol

1.1 Identification

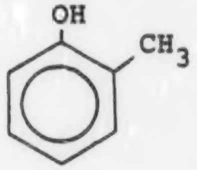
CAS No. 000095487
NIOSH No. GO63000

1.2 Synonyms and Trade Names

o-Cresylic acid; *o*-methyl phenol; 2-methyl phenol; orthocresol; 1-hydroxy-2-methylbenzene; *o*-hydroxytoluene; *o*-methylphenol; *o*-oxytoluene; 2-hydroxytoluene

(G16)

1.3 Chemical Formula and Molecular Weight



C_7H_8O Mol. Wt. 108.15

(G22)

1.4 Chemical and Physical Properties

1.4.1 **Description:** White crystals; phenol-like odor; combustible; becomes dark with age and exposure to air and light. (G23,G21)

1.4.2 **Boiling Point:** 190.95° C (G22)

1.4.3 **Melting Point:** 30.94° C (G22)

1.4.4 **Absorption Spectrometry:**

$$\lambda_{\text{Max}}^{\text{Water}} = 219,\ 275 \text{ nm}$$

$$\log \epsilon = 3.71,\ 3.22$$

(G22)

1.4.5 **Vapor Pressure:** 1 mm at 38.2° C (G22)

1.4.6 **Solubility:** Soluble in water and ordinary organic solvents; Very soluble in alcohol and ether; Soluble in all proportions in acetone, benzene, carbon tetrachloride

(G22)

1.4.7 Octanol/Water Partition Coefficient:

$$\text{Log } P_{oct} = 3.40$$ (G15)

1.5 Production and Use

1.5.1 Production:

49.700	Million lbs	(1972)	(G28)
20.481	Million lbs	(1975)	(G24)
22.187	Million lbs	(1976)	(G24)

1.5.2 Use: Disinfectant; solvent (G23)

1.6 Exposure Estimates

1.6.1 Release Rate: 15.6 Million lbs (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 1480

Estimates no. of persons exposed: 52,000*

*rough estimate (G29)

1.7 Manufacturers

from coal tar:

Koppers Co., Inc.
Ferro Corp.

from petroleum:

Merichem Co.
Ferro Corp.
Sherwin-Williams Co.

(G24)

CRESOLS

IV. p-Cresol

1.1 Identification

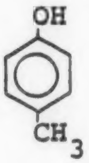
CAS No.: 000106445
NIOSH No.: GO64750

1.2 Synonyms and Trade Names

4-Cresol; p-cresylic acid; 1-hydroxy-4-methylbenzene; p-hydroxytoluene; 4-hydroxytoluene; p-kresol; 1-methyl-4-hydroxybenzene; p-methylphenol; 4-methylphenol; p-oxytoluene; para-cresol; paramethyl phenol

(G16)

1.3 Chemical Formula and Molecular Weight



C_7H_8O Mol. wt. 108.15

(G22)

1.4 Chemical and Physical Properties

1.4.1 **Description**: Crystalline mass; phenol-like odor (G21)

1.4.2 **Boiling Point**: 201.9° C (G22)

1.4.3 **Melting Point**: 34.8° C (G22)

1.4.4 **Absorption Spectrometry**:

$$\lambda_{max}^{cyclohexane} = 280 \text{ nm}$$

$$\log \epsilon = 3.23$$

(G22)

1.4.5 **Vapor Pressure**: 1 mm at 53.0° C (G22)

1.4.6 **Solubility**: Slightly soluble in water;
Soluble in hot water, organic solvents;
Soluble in all proportions in alcohol, ether, acetone, benzene and carbon tetrachloride

(G22)

1.4.7 **Octanol/Water Partition Coefficient**

$$\text{Log } P_{oct} = 2.35$$

(G15)

1.5 Production and Use

1.5.1 Production:

No information found in sources searched

1.5.2 Use:

As a chemical intermediate (G24)

1.6 Exposure Estimate

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure

Rank: 2466

Estimated no. of persons exposed: 14,000*

*rough estimate

(G29)

1.7 Manufacturers

Sherwin-Williams Co.

(G24)

CRESOLS

SUMMARY OF CHARACTERISTICS

Name	Solubility	Log P_{oct}	Estimated Environmental Release (Million lbs)	Production (Million lbs)	Estimated no. of persons exposed (occupational)	Use
Cresol (mixed isomers)	s in alc, glycol, dil. alk, eth, chl. ss in H_2O	2.70	30.4	~60 (1968) ~80 (1973)	1,914,000	Disinfectant; phenolic resins; tricresyl phosphate; ore flotation; textile scouring agent; organic intermediate; mfg. of salicylaldehyde, coumarin, and herbicides; surfactant
o-Cresol	s in H_2O and OOS. vs in alc and eth. ∞ in ace, bz, CCl_4.	3.40	15.6	49.7 (1972) 20.481 (1975) 22.187 (1976)	~ 52,000	Disinfectant, solvent
m-Cresol	ss in H_2O; s in hot H_2O, os; ∞ in alc, eth, bz, ace, CCl_4	2.37	*	*	~ 9,000	In disinfectants, fumigants, photographic developers, explosives
p-Cresol	ss in H_2O; s in hot H_2O, os; ∞ in alc, eth, bz, ace, CCl_4	2.35	*	*	~ 14,000	cyclic intermediate

* No information found in sources searched.

CRESOLS

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

Log octanol/water partition coefficients are 3.40, 2.37, and 2.35 for the o-, m-, and p-isomers, respectively (G15). The high partition coefficient of the o-isomer is due to the steric effect of the methyl group on the hydroxyl group. The high octanol/water partition coefficients of the cresols indicate that bioaccumulation in aquatic organisms is a possibility, but specific data on such bioaccumulation are not available. By analogy with phenol, which appears to be completely eliminated from the body within 24 hours (G19), it is expected that cresols would not be bioaccumulated in mammals. Cresols in waste waters near industrial plants are reported to undergo rapid biodegradation (G14), which indicates that cresols, like phenol, are relatively easily metabolized.

2.2 Contaminants and Environmental Degradation or Conversion Products

Cresols are sold in a wide variety of technical and special grades, classified by color and distillation range (G25). The composition of the various materials depends upon the starting material and the method of production. A major source of cresols is the tar-acid oil obtained as a by-product of coking of coal (G25).

Cresols (boiling above 204°C), available as a mixture of o-, m-, and p-isomers from tar acids are called cresylic acid. A less refined product called creosote oil contains 10-20% by volume of the tar from the coking process; it is used as a wood preservative (G25). Creosote oil may contain polynuclear aromatic hydrocarbons. Xylenols and phenol are common impurities (or ingredients) of technical grade cresols (G25).

The high environmental stability of the cresols in soils (owing to their antimicrobial properties) contributes to their widespread use as wood perservatives. o-Cresol is degraded by the hydroxyl radical and ozone in air and by organic peroxide radicals in water; half life estimates are less than 1 day in air and 10 days in water (G14). The m- and p-isomers are expected to behave similarly. Environmental degradation is likely to be by air oxidation to give quinones and dihydroxybenzenes (G14).

Biodegradation products of cresols by sewage microorganisms include carbon dioxide, methane, 3-methylcatechol, 2-hydroxy-6-oxahepta-2,4-dienoic acid, oxalic acid, pyrocatechol,carboxylic acid, and salicylic acid (G14). By analogy with phenol, cresols may be methylated in the environment to form the corresponding anisoles.

2.3 Acute Toxicity

The NIOSH Registry of Toxic Effects of Chemical Substances (G16) reports the acute toxicity of cresols as follows:

Substance	Parameter	Dosage	Animal	Route
Cresol	LD50	1454 mg/kg	rat	oral
	LD50	861 mg/kg	mouse	oral
o-Cresol	LD50	121 mg/kg	rat	oral
	LD50	1100 mg/kg	rat	skin
	LD50	344 mg/kg	mouse	oral
	LDLo	410 mg/kg	mouse	subcutaneous
	LDLo	55 mg/kg	cat	subcutaneous
	LDLo	940 mg/kg	rabbit	oral
	LD50	1380 mg/kg	rabbit	skin
	LDLo	450 mg/kg	rabbit	subcutaneous
	LDLo	180 mg/kg	rabbit	intravenous
	LDLo	360 mg/kg	guinea pig	intraperitoneal
	LDLo	200 mg/kg	frog	subcutaneous
m-Cresol	LD50	242 mg/kg	rat	oral
	LD50	620 mg/kg	rat	skin
	LD50	350 mg/kg	rat	unknown
	LD50	828 mg/kg	mouse	oral
	LDLo	450 mg/kg	mouse	subcutaneous
	LDLo	180 mg/kg	cat	subcutaneous
	LDLo	1400 mg/kg	rabbit	oral
	LD50	2050 mg/kg	rabbit	skin
	LDLo	500 mg/kg	rabbit	subcutaneous
	LDLo	280 mg/kg	rabbit	intravenous
	LDLo	100 mg/kg	guinea pig	intraperitoneal
	LDLo	250 mg/kg	frog	subcutaneous

(continued)

Substance	Parameter	Dosage	Animal	Route
p-Cresol	LD50	207 mg/kg	rat	oral
	LD50	705 mg/kg	rat	skin
	LD50	344 mg/kg	mouse	oral
	LDLo	150 mg/kg	mouse	subcutaneous
	LD50	160 mg/kg	mouse	unknown
	LDLo	80 mg/kg	cat	subcutaneous
	LDLo	620 mg/kg	rabbit	oral
	LD50	301 mg/kg	rabbit	skin
	LDLo	300 mg/kg	rabbit	subcutaneous
	LDLo	180 mg/kg	rabbit	intravenous
	LDLo	100 mg/kg	guinea pig	intraperitoneal
	LDLo	150 mg/kg	frog	subcutaneous

Cresols are rated as moderately toxic to humans (G4). Acute exposures can cause muscular weakness, gastroenteric disturbances, severe depression, collapse, and death (G38). Organs attacked by cresols include the central nervous system, liver, kidneys, lungs, pancreas, spleen, eyes, heart, and skin (G38). The type of exposure to cresols determines, in part, the toxic effects. Cresols are highly corrosive to any tissues they contact (G5) and are readily absorbed by skin and mucous membranes. Systemic effects, including death, occur after dermal exposure. Because their vapor pressure is low at 25°C, cresols do not usually constitute an acute inhalation hazard. No data are available on the toxicity of cresol vapors to humans (G39).

In animals, cresol toxicity varies with the isomer, the species and the route of exposure. Reported LD50s vary from a low of 121 mg/kg in the rat (oral, o-cresol) to a high of 2050 mg/kg in the rabbit (skin, m-cresol) (G16). Evidence for different biological effects of the three isomers includes the observation that the ratios between the LD50s of the least toxic and most toxic isomers vary from as low as 1.8 (cutaneous, rat) to as high as 6.8 (cutaneous, rabbit). Furthermore, p-cresol, but neither o- nor m-cresol, produced permanent pigment loss in the hair of mice (1).

2.4 Other Toxic Effects

Chronic poisoning from absorption of cresols through the skin, mucous membranes or respiratory tract has not been well studied. Campbell (2) presented incomplete studies showing that exposure of mice to an atmosphere saturated with cresylic acid vapors for 1 hr/day on consecutive days caused irritation of the nose and eyes, and death in some animals. Uzhdavini et al. (3) performed poorly documented studies on the chronic effects of o-cresol inhalation. In mice, they found evidence for: tail necrosis; slowed weight gain; cellular degeneration of the CNS; respiratory tract hyperemia, edema, proliferation of cellular elements, and hemorrhagic patches; myocardial fiber degeneration; and protein deposits in liver and kidney cells. In rats, they reported alterations in a conditioned reflex, and alterations in both peripheral blood and bone marrow elements.

The Threshold Limit Value established by the ACGIH for cresols is 5 ppm (G11).

2.5 Carcinogenicity

o, m, and p-Cresol have been reported to promote the carcinogenicity of dimethylbenzanthracene (DMBA) in skin tests with mice (4). They were slightly less active as promoters than phenol in this experiment (see table below).

Promoter*	No. mice survivors/ original no.	Avg. no. papillomas per survivor	% survivors with papilloma
Benzene Control	12/12	0	0
20% phenol	22/27	1.50	64
20% o-cresol	17/27	1.35	59
20% m-cresol	14/29	0.93	50
20% p-cresol	20/28	0.55	35

* Initiator: 0.3% DMBA in acetone. Promoter in benzene. Data at 12 weeks.

No carcinogenicity tests conducted with cresols alone have been found in the searched literature.

2.6 Mutagenicity

In onion root tips, *m*- and *p*-cresol produced cytological abnormalities including stickiness, erosion, pycnosis, *C*-mitosis, polyploidy, and chromosome fragmentation (5). *o*-Cresol did not appear as active (5). These chromosomal effects do not necessarily imply that the cresols will have genetic activity in mammals. No other mutagenicity studies were found in the searched literature.

2.7 Teratogenicity

No systematic studies of the teratogenic potential of the cresols have been found. The only information available is on the effect of *m*-cresol on embryos of a toad (*Xenopus laevis*) at the neural tube stage of development (6). Concentrations of 20 to 80 ppm, *m*-cresol caused two developmental abnormalities: edema and tail flexion.

2.8 Metabolic Information

Very little is known about the metabolic fate of cresols in mammals. One study showed that the cresols are excreted in rabbit urine primarily as oxygen conjugates: 60-72% as ether glucuronides and 10-15% as ethereal sulphates (7). Paper chromatography showed that *o*- and *m*-cresol are hydroxylated and that *p*-cresol forms *p*-hydroxybenzoic acid (7). *p*-Cresol glucuronide was isolated from the urine of rabbits dosed by stomach tube with *p*-cresol, whereas *o*- and *m*-cresol were metabolized to 2,5-dihydroxytoluene (7). No studies have been traced of the biological effect of these and other possible metabolites of the cresols.

2.9 Ecological Effects

The 96-hour LC50 of o-cresol to channel catfish (Ictalurus punctatus) is reported to be 67 mg/l (8). In tests with perch and sunfish, lethal concentrations (not LC50s) were determined in 1 hour exposures. In perch (Perca fluviatilis), lethal concentrations for o-, m- and p-cresols were in the range 10-20 ppm (9). The Aquatic Toxicity Rating (96-hour TLm, species unspecified) for cresols is listed as 10-1 ppm (G16). Although o-cresol is less toxic to juvenile Atlantic salmon (Salmo salar) than p-cresol, the salmon avoided o-cresol more efficiently (10).

Cresols have a broad spectrum of toxicity to microorganisms. They are used as disinfectants and as fungicides to protect materials such as wood. They are also reported to be active against mycoplasmas (11), viruses (12), and plant galls (13).

2.10 Current Testing

A criteria document on cresols is planned for completion in 1977 by NIOSH.

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HEXACHLORO-1,3-BUTADIENE

TABLE OF CONTENTS

Page

Overview VII-1

Part I - General Information VII-3

Specific References VII-5

Part II - Biological Properties

2.1 Bioaccumulation VII-6

2.2 Contaminants and Environmental Degradation or Conversion Products VII-9

2.3 Acute Toxicity VII-10

2.4 Other Toxic Effects VII-12

2.5 Carcinogenicity VII-15

2.6 Mutagenicity VII-15

2.7 Teratogenicity VII-15

2.8 Metabolic Information VII-15

2.9 Ecological Effects VII-15

2.10 Current Testing VII-17

References VII-19

HEXACHLORO-1,3-BUTADIENE

AN OVERVIEW

Hexachloro-1,3-butadiene (HCBD) is a clear colorless liquid with a mild odor. It is insoluble in water but soluble in alcohol and ether. It is an unreactive compound, stable to acids and alkalis and extremely resistant to hydrolysis.

HCBD is not known to have been produced commercially in the United States since 1970, but is imported into the U.S. for industrial solvent use, mainly from West Germany. HCBD is a waste product in the manufacture of chlorinated solvents such as perchloroethylene, trichloroethylene, and carbon tetrachloride. It occurs in tarry wastes with hexachlorobenzene and other chlorinated by-products.

Some of the uses of HCBD are as a solvent for elastomers, as an agent for the recovery of chlorine from gas streams in chlorine plants, as a heat transfer liquid and as a chemical intermediate in the manufacture of rubber compounds.

HCBD has been reported to bioaccumulate in fish and other aquatic organisms. The release of HCBD into the environment has not been quantified, but there is evidence that it may be widely distributed in the aquatic environment. No incidents of ecological damage caused by HCBD have been reported. However, it is toxic to fish at low concentrations. Its use as a pesticide in overseas countries provides further indication of its biological activity.

HCBD is moderately toxic to mammals: reported LD50 values in several species are in the range 65-350 mg/kg. A number of studies of subacute and chronic toxicity of HCBD have been published, primarily in the Russian literature. HCBD causes pathological changes in the kidney, liver, central nervous system, and lungs of the offspring. Adverse effects on reproduction in rats have been reported in one study.

HCBD is mutagenic in the Salmonella reversion test with microsomal activation. No adequate carcinogenicity tests and no teratogenicity or metabolic studies have been traced. Studies of chronic oral toxicity, carcinogenicity, and effects on reproduction are in progress.

HEXACHLORO-1,3-BUTADIENE

PART I

GENERAL INFORMATION

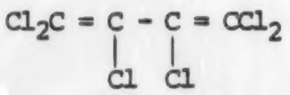
1.1 **Identification** CAS No.: 000087683
NIOSH No.: EJ07000

1.2 Synonyms and Trade Names

HCBD; C-46; hexachlorobutadiene; hexachlorbutadiene

(G16)

1.3 Chemical Formula and Molecular Weight



$$Cl_2C=C(Cl)-C(Cl)=CCl_2$$

C_4Cl_6 Mol. wt. 260.76

(G22)

1.4 Chemical and Physical Properties

1.4.1 **Description:** Clear, colorless liquid with mild odor; nonflammable (G21)

1.4.2 **Boiling Point:** 215° C (G22)

1.4.3 **Melting Point:** -21° C (G22)

1.4.4 **Absorption Spectrometry:**

$$\lambda_{max}^{Heptane} = 253 \text{ nm}$$

$$\log \epsilon = 3.7$$

(G22)

1.4.5 **Vapor Pressure:**

0.15 mm at 20° C (1)

1.4.6 **Solubility:** Insoluble in water;
Soluble in alcohol and ether

(G22,G21)

1.4.7 **Octanol/Water Partition Coefficient:**

No information found in sources searched (G36)

1.5 Production and Use

1.5.1 **Production:** Hexachlorobutadiene has not been produced in the U. S. since 1970 because of low domestic demand. Imported hexachlorobutadiene is available in the U.S. - see 1.7 Suppliers

(2)

1.5 Production and Use (Continued)

1.5.2 Use: As a solvent for elastomers; as a heat transfer liquid; in transformer and hydraulic fluid; in wash liquor for removing C_4 and higher hydrocarbons; for recovery of chlorine-containing gas; as a chemical intermediate in the manufacture of rubber compounds (G21, 2)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure:

No information found in sources searched

1.7 Suppliers:

Davos Chemical Corp.
Kay-Fries Chemicals, Inc.
Rhodia, Inc.

(G37)

Specific References for Part I

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HEXACHLORO-1,3-BUTADIENE

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

Hexachloro-1,3-butadiene (HCBD) is a water-insoluble, stable compound. Several reports on its propensity to bioaccumulate were found. In one report on aquatic fauna from the IJsselmeer, IJssel River, and the Ketelmeer (all in The Netherlands and fed by industrial waters of the River Rhine), HCBD levels in fish and other aquatic animals were found to be about 1,000 times higher than the concentration in the waters of the Ketelmeer (a lake) (1). Thus, HCBD levels in fish (perch, pike, tench, common bream, white bream, and roach) ranged from 0.13 ppm to 1.86 ppm, while the level of HCBD in the water was 0.13 ppb. Similar elevated levels of HCBD (0.03 to 2.41 ppm) were noted in molluscs (*Lymnaca peregra* and *Sphaerium* spp.), oligochaete worms (mainly *Limnodrilus* spp.) and detritus (1). However, the data indicated that bioaccumulation via food chains to higher trophic levels did not occur.

In another study, chemical pollutants known to be present in the River Rhine (HCBD; hexachlorobenzene; 1,2,3,4- and 1,2,3,5-tetrachlorobenzene; 1,3,5-trichlorobenzene; *o*-dichlorobenzene; and lindane) were fed as a mixture to albino rats (2). HCBD was stored at low levels. Of the 7 compounds fed, HCBD accumulated least as shown by analyses of abdominal and renal fat (2).

HCBD has been found in fish of the lower Mississippi River basin at levels that ranged from 0.01 to 1.2 ppm in one study (3) and from a trace to 4.65 ppm in another (4). The concentration of HCBD in the water was not determined.

A Russian investigator stated that HCBD has cumulative properties (5), while another Russian author stated that cumulative properties are rather weak (6).

Tables 1 and 2 summarize the results of laboratory bioaccumulation tests with fish and mussels exposed to about 1.5 ppb HCBD (7). Bioaccumulation factors were 500 - 700 in the flesh of fish (dabs and plaice) and 7,000 - 10,000 in their livers. In mussels, the factors were 900 - 2,000 in the whole animals. To check food-chain accumulation, HCBD-contaminated mussels were fed to plaice for 88 days but no accumulation occurred (Table 1).

In another experiment, removal of contaminated fish to water free of HCBD resulted in almost complete loss of HCBD in 30 - 40 days (7).

TABLE 1

ACCUMULATION OF HEXACHLOROBUTADIENE BY DABS AND PLAICE (7)

Species	tissue analysed	period of exposure days	mean exposure concentration, parts/10^6	mean concentration in tissues, parts/10^6	accumulation factor
dab	flesh	27-39	0.0016	1.1 (6)	x 700
	liver	27-39	0.0016	20.0 (6)	x 10000
plaice	flesh	21-106	0.0017	0.78 (10)	x 500
	liver	21-106	0.0017	12.1 (9)	x 7000
plaice	flesh	19-88*	1.8**	0.04 (15)	≪ 1
	liver	19-88*	1.8**	0.66 (15)	< 1

Numbers in parentheses are number of specimens analysed.

*Fed to fish in food

**These concentrations are mean values for mussels which were fed to the plaice after having been previously exposed to HCBD in sea water.

TABLE 2

ACCUMULATION OF HEXACHLOROBUTADIENE BY MUSSELS (7)

tissue analysed	period of exposure, days	mean exposure concentrations, parts/10^6	mean concentration in tissues, parts/10^6	accumulation factor
whole	38	0.0013	2.55 (10)	x 2000
whole	50	0.0016	1.37 (5)	x 900
foot	21-106	0.0017	0.82 (10)	x 500
gill	21-106	0.0017	1.73 (10)	x 1000
gonad	21-106	0.0017	3.92 (10)	x 2000
digestive gland	21-106	0.0017	5.52 (10)	x 3000

Numbers in parentheses are the numbers of specimens analysed.

The laboratory accumulation factors in the aquatic organisms were similar to those found in these organisms taken from industrial waters (Liverpool Bay, England) (7).

Table 3 shows the concentrations of HCBD found in algae (Oedogonium cardiacum) exposed to water containing 16.9 ppb HCBD in a continuous flow experiment (25).

TABLE 3

ACCUMULATION OF HCBD BY ALGAE (25)

days exposure	HCBD in algae (ppb)	accumulation factor
1	966	x 57
3	2547	x 150
7	2701	x 160

Adsorption of HCBD to sediments was shown in another continuous-flow experiment in which sediments were exposed to water containing 3.6 ppb HCBD. The concentration of HCBD in sediments was 725 ppb after 1 day of exposure, 938 ppb after 4 days exposure, and 632 after 4 days in clean water (25).

In summary, HCBD does bioaccumulate, particularly in fish located in HCBD-contaminated waters. However, two reports indicated that HCBD did not bioaccumulate to higher trophic levels in aquatic organisms via the food chain; also, HCBD was eliminated in 30-40 days from fish placed in HCBD-free water.

2.2 Contaminants and Environmental Degradation or Conversion Products

Owing to low demand, HCBD has not been produced in the U.S. since 1970, and only 200,000-500,000 lb/yr are imported for domestic needs (8). However, about 11 million lb/yr are generated annually in distillation residues as a by-product of the production of perchloroethylene, tricholoroethylene, and carbon tetrachloride. About 98% of the by-product is disposed of in land fills or by incineration; the remaining HCBD is lost to the environment via air and water, about 1% to each (8). A major concern is that HCBD will contaminate the environment and ultimately the food supply (4).

HCBD is reactive toward OH radical and ozone with half-lives less than 1 day; the half-life toward peroxy radical is 1000 days (G14). In laboratory tests, the half-life of HCBD vapor exposed to outdoor light was quite short, about 1 week. The major product of degradation of the compound exposed to light simulating that in the troposphere was identified as HCl (95%) (7). However, traces of HCBD have been found in ambient air (G14).

Breakdown of HCBD in water appears to be very slow. Owing to its structure and low vapor pressure, HCBD is adsorbed on sediments and is transferred to the air slowly (7).

A Midwest Research Institute report (8) states that HCBD is a "potentially hazardous environmental pollutant that is resistant to chemical degradation." HCBD is stable to acids and alkalis and extremely resistant to hydrolysis. The lack of reactivity of the molecule is evident from its high thermal stability, with a half-life at 380° C of 53 hours (9). Oxidation of HCBD requires exposure to oxygen between 110-210° C (10). In Europe, the compound has been found in fruit juices, wine, and run-off waters (G14), which is indicative of its persistence.

2.3 Acute Toxicity

The NIOSH Registry of Toxic Effects of Chemical Substances (G16) reports the acute toxicity of HCBD as follows:

Parameter	Dosage	Animal	Route
LD50	90 mg/kg	rat	oral
LD50	110 mg/kg	mouse	oral
LDLo	235 ppm/4H	mouse	inhalation
LDLo	32 mg/kg	mouse	intraperitoneal

The results of toxicity tests with HCBD conducted by Hazelton Laboratories, Washington, D.C. for the Diamond Shamrock Corporation have been reported in a secondary source (8) as follows:

The acute oral LD50 of HCBD for male albino rats is 178 μl/kg of body weight. At a dosage level of 100 μl/kg none of a group of five animals succumbed. At a level of 316 μl/kg, all of a group of five animals succumbed within 2 days.

The acute dermal LD50 of HCBD for albino rabbits of either sex is 1,780 μl/kg of body weight. After an exposure period of 24-hr, none of a group of four rabbits succumbed at a dosage level of 1000 μl/kg. At a dosage level of 3,160 μl/kg, all of a group of five rabbits succumbed within a period of 5 days. The exposed skins of all animals showed a mild to moderate degree of erythema. This completely subsided by the second or third day and thereafter showed no gross signs of dermal irritation.

A single application of HCBD to the eyes of a group of three albino rabbits of either sex produced a mild degree of irritation which completely subsided within 24 hours. There was no evidence of systemic toxicity from mucous membrane absorption.

Reference 8 also gives details of acute inhalation toxicity tests concluded by Hazelton Laboratories. Mice, rats, and guinea pigs exposed to an aerosol of HCBD at approximately 6,800 ppm (73 g/m^3) died after periods ranging from 165-357 minutes.

Murzakaev, a Russian investigator (11), determined the acute oral LD50s of HCBD to be as follows:

Parameter	Dosage	Animal	Route
LD50	87 mg/kg	mouse	oral
LD50	350 mg/kg	rat	oral
LD50	90 mg/kg	guinea pig	oral

Gradiski et al. (12) have reported the LD50 by oral and intraperitoneal routes for female and male mice and rats as follows:

Route of Administration	LD50, mg/kg			
	Mice		Rats	
	Female	Male	Female	Male
Intraperitoneal	76±5	105±15	175±25	216±6
Oral	65±5	80±5	270±20	250±30

HCBD has a mild irritant action on the skin and ocular mucous membranes of rabbits. It produces marked skin reaction on guinea pigs (12).

2.4 Other Toxic Effects

The subacute inhalation toxicity of HCBD has been reported by Gage (15) as follows in rats (4 male and 4 female):

Dosage	Exposure Time	Effects
250 ppm	2 x 4 hr exposures	Eye and nose irritation, respiratory difficulty, females affected more than males, apparent recovery after exposure; autopsy (histol.), degeneration of middle renal proximal tubules and of adrenal cortex
100 ppm	12 x 6 hr exposures	Eye and nose irritation, respiratory difficulty, poor condition, weight loss, slight anemia in females, urine tests normal, 2 females died; autopsy, kidneys pale and enlarged, degeneration of renal cortical tubules with epithelial regeneration

Subacute inhalation toxicity of HCBD (Continued):

Dosage	Exposure Time	Effects
25 ppm	15 x 6 hr exposures	Poor condition, diminished weight gain in females; respiratory difficulty, blood and urine tests normal; autopsy, kidneys pale and enlarged, (histol.) damage to renal proximal tubules
10 ppm	15 x 6 hr exposures	Retarded weight gain in females; autopsy, organs normal
5 ppm	15 x 6 hr exposures	No toxic signs; autopsy, organs normal

The results of a preliminary behavioral study on mice suggest that hexachlorobutadiene has effects on the central nervous system. Morphological, hematological and biochemical tests revealed hepatic and renal disorders in laboratory animals (mice, rats, guinea pigs, and rabbits) (12).

The remainder of information in this section is compiled from abstracts of papers appearing in Russian journals.

Rats and guinea pigs fed 0.004, 0.04, 2 and 7 mg/kg HCBD showed a decrease in the sulfhydryl (SH) groups in the blood serum after 3 months at the 2 mg/kg level. Rats fed 7 mg/kg showed a decrease in the SH level in the gray matter of the brain and a functional change in CNS activity (19). Female rats fed 7.0 mg/kg for 6 months showed disrupted ability to form conditioned reflex pathways, decreased SH group content in the blood and brain, and morphological changes in the liver, kidneys, and cardiac muscle (6).

In inhalation, oral, and topical treatments, HCBD was found to be a polytropic poison in rats, mice, guinea pigs and cats. The following effects were noted:

Leucocytosis and lymphocytosis along with a decreased erythrocytic osmosis resistance

Displacement of the pH towards acidosis along with decreased Vitamin B_1 and C levels in the internal organs

Increased residual serum nitrogen and decreased total blood protein levels along with enhanced internal organ transaminase, decreased blood peroxidase and catalase activities

Immunological depression including decreased antibody formation potentials along with reduced neutrophil and reticulendothelial phagocytic capacities (5)

Oral treatment of rabbits in subacute (10 mg/kg daily for 10 days) or chronic (1 mg/kg daily for 90 days) exposures is stated to have caused "metabolic acidosis" (13, 14).

Chronic poisoning due to HCBD may cause protein denaturation and necrotic nephrosis followed by auto-sensitization and the development of autoallergic glomerulonephritis as an end result. HCBD at 8.4 mg/kg caused dystrophic changes in kidneys and at 10 mg/kg caused necrosis (16).

HCBD administered orally to puppies at 0.05 mg/kg daily for 45 days (from 1.5 to 3 months postnatal) increased the amounts of HCl and chloride secreted by the stomach and caused irritation of the gastric mucosa. Respiration, body temperature and growth rate were not affected (17).

The effects of HCBD on reproduction in albino rats have been reported by Poteryaeva (20). Subcutaneous administration to female rats at a dosage of 20 mg/kg led to lowered vitality, reduced weight gain and loss of motor coordination in their offspring. Pathological changes in the lungs, liver, kidneys, and gastrointestinal tract were also reported. All the offspring of the rats which had received HCBD died within three months of birth. Offspring of rats given a higher dose level (70-150 mg/kg either orally or subcutaneously) died within two months of birth (20).

2.5 Carcinogenicity

This compound has been tested orally in guinea pigs and rats for 7 months. No tumors were reported but liver and kidney damage was observed (19).

2.6 Mutagenicity

Hexachlorobutadiene is reported to be mutagenic in the *Salmonella typhimurium* reversion test in strain TA100, with rat liver microsome activation (26).

2.7 Teratogenicity

No reports of teratogenicity tests in mammals have been found in the searched literature. In a reproduction study in Japanese quail, no morphological abnormalities were found in chicks hatched from eggs laid by females exposed to HCBD at 30 ppm in the diet (21).

2.8 Metabolic Information

No information found in searched literature.

2.9 Ecological Effects

In the United States, environmental contamination with HCBD originates primarily from its generation as a by-product in the manufacture of other chemicals, mainly perchloroethylene (see Section 2.2). Much of this by-product is buried in landfills, which constitute a potential pollution source. A recent survey disclosed that eggs and vegetables produced near perchloroethylene plants are not likely to be contaminated with HCBD (3). However, HCBD residues (0.01-1.2 ppm) were found in freshwater fish from the lower Mississippi River (3, 4). In an English survey, levels of HCBD in fish and aquatic organisms were generally non-detectable, although some were in the 2-5 ppb range (7). The average and maximum concentrations of HCBD in water from the Liverpool Bay area were 0.004 and 0.03 ppb, respectively (7). In marine sediments from the same bay, HCBD concentrations were in the range 0.02-8.0 ppm (7). Residues of HCBD in fish, molluscs, and other organisms in polluted waters in the Netherlands were in the range 0.13-2.41 ppm (see Section 2.1).

HCBD is toxic to insects and fungi and has been used as a soil fumigant in some European countries. It is used in the USSR as an insecticide, primarily to combat grape phylloxera (8). These uses may be a source of food contamination. Indeed, HCBD has been found in fruit juices and wine in Europe (G14).

Although no incidents of ecological damage from HCBD have been reported, the following information is pertinent.

96-hr LC50 values for HCBD were reported as 0.09 ppm in goldfish, 0.13 ppm in a crustacean (Asellus aquaticus) and 0.21 in a mollusc (Lymnaea stagnalis). Acute and semichronic intoxication with HCBD in goldfish produced body-weight loss, abnormal behavior, and incoordination. Relative liver weight was increased by exposure to 9.6 ppb, and activities of liver phenylalanine hydroxylase and glucose 6-phosphatase decreased. A no-toxic-effect level was reported to be 3 ppb in semichronic exposures (12).

The 96-hr LC50 of HCBD was 0.45 mg/l for dabs (marine fish) and the 48-hr LC50 of HCBD was 0.87 mg/l for barnacle nauplii (7).

In a reproduction study in Japanese quail fed HCBD at levels up to 30 ppm for 90 days, no effects were observed on body weight, demeanor, food consumption, egg production, percent fertility and hatchability of eggs, survival of hatched chicks, or eggshell thickness. In addition, there were no gross or histopathologic changes in the organs or tissues of the birds that could be related to treatment (21).

2.10 Current Testing

The following studies are recently completed or in progress.

(A) Chronic oral toxicity of hexachlorabutadiene in rats. By Toxicology Research Laboratory, Health and Environmental Research, Dow Chemical Company, Midland, Michigan 48640. The studies involve determination of the toxicological effects from long-term ingestion of graded doses of HCBD in the diet of Sprague-Dawley rats. Pathology is being completed and a report is being drafted, according to Tox-Tips (23). Principal investigator - Dr. R. J. Kociba or Dr. B.A. Schwetz.

(B) Carcinogenesis study of hexachlorobutadiene. By New York University Medical Center, New York, N.Y. 10016. (Investigators-Dr. B. Van Duuren et al., supported by the National Science Foundation). This compound is being tested as an initiator, promoter and complete carcinogen using two-stage skin tests in female ICR/HA mice. Long-term tests began in September and October, 1976, and are expected to continue for the life span of the mice (24).

(C) One-generation reproduction study of rats maintained on diets containing hexachlorobutadiene. By Toxicology Research Laboratory, Health and Environmental Research, Dow Chemical Company, Midland, Michigan, 48640. The purpose of this study is to determine the effects of diets containing various amounts of HCBD on reproduction. The project is completed and a report is being prepared for publication*, according to Tox-Tips (23). Principal investigator - Dr. B. A. Schwetz.

(D) A carcinogenicity study in A-strain mice by i.p. administration is in progress at the Veterinary Sciences Division, Litton Bionetics, Inc., Kensington, Md. 20795 (G13). Principal investigators - Dr. M. Shimkin and G. Stoner.

(E) A carcinogenicity study in rats (Sprague-Dawley) by administration in the diet is in progress at Toxicology Research Laboratories, Health and Environmental Research, Dow Chemical Co. Midland, Michigan 48640 (G13). Principal investigator - Dr. C. G. Humiston.

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* This report appeared after the October 1977 TSCA/ITC report to the EPA Administrator; Schwetz, B.A., Smith, F.A., Humistan, C.G., Quast, J.F. and Kocba, R.J. Results of a reproduction study in rats fed diets containing hexachlorobutadiene. Toxicol. Appl. Pharmacol. 42(2): 387-398 (1977).

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NITROBENZENE

TABLE OF CONTENTS

Page

Overview VIII-1

Part I - General Information VIII-3

Part II - Biological Properties

- 2.1 Bioaccumulation VIII-5
- 2.2 Contaminants and Environmental Degradation or Conversion Products VIII-5
- 2.3 Toxicity VIII-6
- 2.4 Carcinogenicity VIII-8
- 2.5 Mutagenicity VIII-8
- 2.6 Teratogenicity VIII-8
- 2.7 Metabolism VIII-9
- 2.8 Ecological Effects VIII-10
- References VIII-20

NITROBENZENE

AN OVERVIEW

Nitrobenzene is a pale yellow liquid which is very soluble in alcohol, ether and benzene and slightly soluble in water.

U.S. production of nitrobenzene in 1976 was about 400 million pounds. Although its predominant use (97 percent of production) is in closed systems in aniline manufacture, nitrobenzene is also an industrial solvent and dye intermediate. General population exposure can arise from environmental release, and from dispersive uses in soaps; woodcleaners; and metal polishes. It is estimated that 19,000 workers are occupationally exposed to nitrobenzene. Its release to the environment has been estimated to be about 20 million pounds annually.

Evidence indicates that nitrobenzene does not bioaccumulate appreciably in aquatic systems. Acute effects have been demonstrated in fish. Nitrobenzene inhibits oxygen utilization and hydrogen sulfide production in sewage microorganisms, inhibits growth in yeast, and is toxic to various soil bacteria and microorganisms.

There are four major reaction sites to nitrobenzene: in the blood, in the central nervous system, in peripheral metabolism, and from skin exposure. Mammalian toxicity effects include heart, liver, kidney, and CNS damage; hemolytic anemia; methemoglobinemia, sulfhemoglobinemia, nitroxyhemoglobinemia; and changes in WBC and RBC. Nitrobenzene is metabolized in humans to p-aminophenol and p-nitrophenol

No adequate information is available on the carcinogenicity and mutagenicity of nitrobenzene; but teratogenic effects of nitrobenzene have been reported in the Russian literature.

NITROBENZENE

PART I

GENERAL INFORMATION

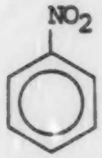
1.1 Identification CAS No.: 000098953
NIOSH No.: DA64750

1.2 Synonyms and Trade Names

C.I. solvent black 5; essence of mirbane; essence of myrbane; mirbane oil; nigrosine spirit soluble B; nitrobenzol; nitrobenzol, liquid; oil of mirbane; oil of myrbane

(G16)

1.3 Chemical Formula and Molecular Weight



$C_6H_5NO_2$ Mol. Wt. 123.11

(G22)

1.4 Chemical and Physical Properties

1.4.1 Description: Greenish-yellow crystals or yellow, oily liquid; combustible; odor of volatile oil of almond (G21,G23)

1.4.2 Boiling Point: 210.8° C (G22)

1.4.3 Melting Point: 5.7° C (G22)

1.4.4 Absorption Spectrometry:

$$\lambda_{max}^{alcohol} = 260 \text{ nm}$$

$$\log \epsilon = 3.91$$ (G22)

1.4.5 Vapor Pressure: 1 mm at 44.4° C (G22)

1.4.6 Solubility: Slightly soluble in water; Very soluble in alcohol, ether, acetone, benzene (G22)

1.4.7 Octanol/Water Partition Coefficient:

$$\log P_{oct} = 1.91$$ (G36)

1.5 Production and Use

1.5.1 Production:

290	Million lbs	(1965)	(G25)
560	Million lbs	(1970)	(G25)
414.288	Million lbs	(1975)	(G24)
409.023	Million lbs	(1976)	(G24)

1.5.2 Use:

In manufacture of aniline; as a solvent for cellulose ethers; in modifying esterification of cellulose acetate; as an ingredient of metal polishes and soaps; in manufacture of benzidine, quinoline, azobenzene, etc.; for refining lubricating oils

(G21,G23)

Quantitative Distribution of Uses:

	Percent
Aniline	97
Miscellaneous	3
	100

(G25)

Consumer Product Information:

Nitrobenzene is present in:

Cleaners for wood paneling, furniture, woodwork, and wood floors
Veterinary liniment

(G35)

1.6 Exposure Estimates

1.6.1 Release Rate: 19.3 Million lbs (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 2184

Estimated no. of persons exposed: 19,000*

* rough estimate (G29)

1.7 Manufacturers

Allied Chemical Corp.
E.I. du Pont de Nemours and Co., Inc.
First Chemical Corp.
Mobay Chemical Company
Monsanto Company
Rubicon Chemicals, Inc.

(G24)

NITROBENZENE

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

Evidence to date indicates that nitrobenzene does not bioaccumulate appreciably in aquatic systems. Thus, labeled nitrobenzene has been tested by adding it to the water phase of an aquatic system which included fish, mosquito larvae, *Daphnia*, snails, algae, and plankton (39). Only in fish (*Gambusia*) was nitrobenzene biomagnified and then only 10-fold. Nitrobenzene was found in the other organisms only at low levels.

2.2 Contaminants and Environmental Degradation or Conversion Products

SRI reports the following contaminants in technical grade nitrobenzene: nitrophenol, dinitrobenzene, and sulfuric acid (G14).

With synthetically prepared sewage effluent, complete biological degradation of dissolved nitrobenzene is obtained (41, as reported in 32). Biological decomposition of nitrobenzenes by *Azotobacter agilis* has been reported in a model waste water system and in laboratory cultures, but the reduction products could not be detected (33). Growing cultures, washed-cell suspensions and cell-free extracts of *Nocardia erythropolis* and *Pseudomonas fluorescens* have also been found to reduce the nitro group to amino, perhaps through the nitroso and hydroxylamino intermediates (5).

Nitrobenzene is relatively unreactive to light (32).

2.3 Toxicity

The NIOSH Registry of Toxic Effects of Chemical Substances (G16) reports the lowest reported lethal doses of nitrobenzene as follows:

Parameter	Dosage	Animal	Route
LDLo	800 mg/kg	rat	subcutaneous
LDLo	400 mg/kg	mouse	skin
LDLo	480 mg/kg	mouse	subcutaneous
LDLo	750 mg/kg	dog	oral
LDLo	150 mg/kg	dog	intravenous
LDLo	2000 mg/kg	cat	oral
LDLo	700 mg/kg	rabbit	oral
LDLo	600 mg/kg	rabbit	skin
LDLo	1000 mg/kg	mammal (unspecified)	oral
TDLo	200 mg/kg	human	oral

There are four major physiological reactions to nitrobenzene: 1. In the blood: The hemoglobin is converted to methemoglobin and thereby is eliminated from the oxygen transport cycle. 2. In the central nervous system: Nitrobenzene causes headache, vomiting, cramps and, in large enough doses, coma. 3. In peripheral metabolism: Metabolic processes degenerate rapidly due to excessive consumption of body substances and high body temperatures. Liver damage and jaundice may result. 4. On the skin: Irritation and sensitization will occur with eczema (G17).

Mild intoxication (10-15% methemoglobin) may produce no symptoms, or a mild headache, a sense of exhilaration, cyanosis of the lips, tongue, or nailbeds. Moderate intoxication (25-50% methemoglobin) causes severe headache, dizziness, weakness and definite cyanosis. Higher intoxication (over 50% methemoglobin) produces severe headache and generalized weakness, nausea, vomiting, drowsiness, shortness of breath on exertion and severe cyanosis. Methemoglobin levels above 65-70% may result in coma. The lethal level of methemoglobin is 85-90% (G5).

Dorigan and Hushon have summarized the reported toxicological effects in humans and animals resulting from nitrobenzene exposure (32). Table I is taken directly from their review.

The anemiagenic action of nitrobenzene is reflected in enlarged spleens and livers, and jaundice (1), (2,37, as reported in 32).

Menstrual disturbances occurred after chronic exposure to nitrobenzene (2, as reported in 32).

Chronic inhalation of small doses by mice resulted in weight loss, anemia, respiration insufficiency and significant changes in oxygen consumption and cerebral enzyme activity (38, as reported in 32).

Chronic nitrobenzene intoxication impairs copper metabolism and certain iron-containing enzyme systems (43, as reported in 32).

Nitrobenzene vapor is readily adsorbed through the lungs. A vapor concentration of 5 mg/m^3 results in an average adsorption rate of up to 18 mg via the lungs and 7 mg cutaneously after six hours of exposure (36). The lung retention rate during six hours of exposure is about 80% (24).

The major source of potential hazard is through cutaneous absorption of nitrobenzene liquid (36). The absorption rate of liquid through the skin can reach about 2 $mg/cm^2/hr$ (40, as reported in 36).

The Department of Transportation has classified nitrobenzene as a Class B Poison (34).

The Threshold Limit Value (TLV)® for nitrobenzene has been set by the ACGIH at 1 ppm (5 mg/m^3) (G11).

2.4 Carcinogenicity

No information found in the searched literature.

2.5 Mutagenicity

A secondary source (G28) reported a Russian experiment to induce sex-linked recessive lethal mutations in *Drosophila melanogaster* when administered as a vapor for 8-10 days. The incidence was 4% of chromosomes analyzed compared to 0.14% of chromosomes from untreated controls. According to the secondary source, the data presented in the original Russian paper were insufficient for evaluation.

2.6 Teratogenicity

Dorigan and Hushon (32) cite a number of Russian studies on the teratogenic potential of nitrobenzene.

Changes in the tissues of the chorion and placenta were reported in pregnant women who worked in the production of a rubber catalyst that uses nitrobenzene (6). Nitrobenzene administered to pregnant rats was reported to cause dead and deformed embryos and changes in respiratory tissues (26, 27). Subcutaneous administration (125 mg/kg) of nitrobenzene to rats during the pre-implantation and placentation periods was reported to cause delay of embryogenesis and the appearance of abnormalities in fetuses, respectively (28). When injected into rats during the period of placentation, glycogen content was reported to increase and polysaccharide composition to change in embryonic and placental tissues (26).

2.7 Metabolism

After intubation (0.25 ml) in rabbits, 54% of the compound was absorbed by the tissues by the second day; in four to five days, 70% was excreted and after eight days only 8% of the dose remained in the rabbit's tissues, mainly as metabolic products. The remainder of the dose was slowly eliminated in urine and exhalation (15).

In another study with rabbits, a labeled dose of nitrobenzene was administered by stomach tube and the metabolites were measured during the next four to five days. 58% of the dose was excreted in the urine as aromatics. The predominant urine metabolites were p-aminophenol (31% of dose) and m- and p-nitrophenol (both 9% of the dose). Another 9% of the dose was excreted in the feces, two thirds of which was p-aminophenol. Two percent of the dose was expired from the lungs as CO_2, aniline and unchanged nitrobenzene. 15%-20% of the radioactivity accounted for was found in the tissues as unspecified metabolic products (15).

Following the ingestion of approximately 50 ml of nitrobenzene by a 19-year old female in an attempted suicide, p-nitrophenol and p-aminophenol were observed in the urine for the next 22 days. A total of 712 mg of p-aminophenol and 1,780 mg of p-nitrophenol were measured in the urine (37, as reported in 32).

A woman exposed to unspecified atmospheric concentrations of solvent vapor (99.7% nitrobenzene, 0.27% benzene) for about six weeks had 1,056 millimoles/ml of p-nitrophenol and 416 millimoles/ml of p-aminophenol in her urine. The metabolites gradually disappeared from the urine during two weeks of hospitalization (1).

Metabolic studies on men exposed to nitrobenzene vapor under experimental conditions have been reported by Piotrowski (36). It was found that about half as much vapor was absorbed through the skin as through the lungs and that *p*-nitrophenol was excreted in the urine in increasing amounts on successive days of exposure and became fairly steady after the third day. In humans, *p*-nitrophenol excreted daily was, on the average, equivalent to 16% of the daily uptake of nitrobenzene, while the efficiency of conversion of nitrobenzene into *p*-nitrophenol in rats was about 23%. When *p*-nitrophenol, itself, was given, excretion was very rapid, but when nitrobenzene was given, *p*-nitrophenol was excreted slowly. Thus, the bioaccumulation observed does not depend on the behavior of the metabolite but is due to the slow rate (kinetics) of metabolism of nitrobenzene. *p*-Aminophenol was not detected in urine under the experimental conditions.

2.8 Ecological Effects

Lethal and other acute effects in fish are mentioned in one Toxline abstract; however the concentrations and types of fish are not reported (14). The aquatic toxicity rating (96-hr TLm, species unspecified) is 100-10 ppm (G16), which is described as slightly toxic.

Effects on aquatic microorganisms have been reported only at relatively high levels. Nitrobenzene decreased the oxygen uptake of benzene-acclimated sludge by 50% when added at 630 mg/l (45, as reported in 32). Hydrogen sulfide production and growth were retarded in sulfate reducing bacteria when nitrobenzene was present at 2-20 ppm (46, as reported in 32). Spores of the yeast *Actinomyces sphaeroides* showed a decrease in viability of 6%-80% following treatment of 0.001-0.004 M nitrobenzene (35, as reported in 32).

Nitrobenzene loss in water effluents from production facilities has been reported (0.09% in one plant, 2% in another) (42,44, as reported in 32).

Nitrobenzene escapes to the atmosphere during industrial production (47, as reported in 32), although this level is considered to be low (32). The ground level concentration 500 meters downwind from the largest production facility was estimated at 1.56 mg/m^3 (32).

NITROBENZENE

Table I

Reported Toxicological Effects

Organism	Dose			Response	Reference
	Route	Concentration	Exposure time		
human	inhalation	-	8 hours/day for 17 months factory worker (paint firm)	cyanosis, headache fatigue methemoglobinemia	1
	inhalation	- (poor ventilation)	8 hours/day for 1.5 months factory worker (paint firm)	cyanosis, headache, fatigue methemoglobinemia, liver damage hypotension	1
			8 hours/day for 4.5 months	above plus: liver and spleen enlarged and tender, hyperalgesia in extremeties	1
	inhalation	0.2-0.5 mg/l (40-100 ppm)	ca. 6 hours	slight effects, e.g., headache, fatigue	2
	inhalation	0.129 mg/m^3	-	threshold level for electroencephalograph disturbance	3
	inhalation	"large" amounts (poor ventilation)		hospitalized: day 1 - fatigue, headache, asthma 2 - vertigo, coma, cyanosis 3 - labored breathing, urine with almond odor, methemoglobinemia 7 - symtoms gone recovery after one month	4

* The contents of this table are quoted directly from Dorigan, J. and Hushon, J. Air Pollution Assessment of Nitrobenzene, MITRE, MTR-7228 (1976).

Organism	Route	Dose Concentration	Exposure Time	Response	Reference
human	inhalation	acute	-	burning throat, nausea, vomiting gastrointestinal disturbances, cold skin, livid face, cyanosis	2
	inhalation	-	- nitrobenzene factory worker	intermittent symptoms: cyanosis, pallor and jaundice, pharyngeal congestion, headache, changes in blood cell composition (increased polynuclears and eosinophils)	2
	inhalation	6-30 μg/l	6 hours	retained 80 percent of vapor in lungs urinary excretion of p-nitrophenol (maximum in 2 hours, still detected after 100 hours)	5
	inhalation	-	- factory worker (rubber accelerator)	pregnant women: thickening of tissue in blood vessels, decreased placental absorption, necrosis in placental tissue	6
	inhalation	-	- factory worker (glass, porcelain)	changes in bone marrow, increased lymphoid cell production, impairment of copper metabolism and certain iron-containing enzymes	7
	inhalation	-	- industrial exposure	disturbance of motor impulses	8
	inhalation	acute	- factory worker (filled containers with nitrobenzene)	14 days: cyanosis, headache, backache stomachache, vomiting ca. 21 days: drank beer and fell unconscious, cyanosis, dilated pupils, retarded respiration, weak pulse 1 year: intelligence dimmed 2 years: emaciated, atrophied muscles 3 years: memory failed 6 years: loss of perception of time and space (Karsakoff's syndrome)	9

Organism	Route	Dose Concentration	Exposure Time	Response	Reference
human	cutaneous absorption	dye used in diaper stamps	-	babies: cyanosis, rapid pulse, shallow respiration, vomiting, convulsions, recovery in 24 hours	2
	cutaneous absorption	shoe dye	ca. 7 hours	unconsciousness after consumption of alcoholic beverages, death	9
	cutaneous absorption	0.5% by weight in paper	- (handled carbon paper)	dermatitis	10
	oral	-	from human milk	nurselings became cyanotic, recovery in 24 hours (mothers ate almond cake artificially flavored with nitrobenzene)	11
	oral	333 ml	one dose	maximum dose with recovery reported (following severe symptoms)	2
	oral	0.4 ml	one dose	minimum lethal dose reported	9
rabbit	subcutaneous injection	0.8 mg/kg	daily	maximum dose not causing death	12
	subcutaneous injection	10-14 mg/kg	one	minimum effective dose: slow and lasting methemoglobinemia	2
	cutaneous absorption	0.7 gm/kg	-	52 hours: lethal	2
	intraperitoneal injection	0.5 gm/kg	one	reduced blood pressure and myocardial glycogen level	13

Organism	Route	Dose Concentration	Exposure Time	Response	Reference
rabbit	intravenous	0.1 gm	daily or every 5 days	simultaneous doses of 2-20 ml ethanol increased severity of poisoning	14
	oral	9 gm	4 doses, one every 15 minutes	convulsions, death	2,9
	oral	4.8 gm	one	lethal instantly	2,9
	oral	700 mg/kg	one	lethal dose	G23
	oral	600 mg	one	dizziness, loss of reflexes, methemoglobinemia, congestion of brain tissue. 12 hours - death	9
	oral	300 mg	one	fatigue for one week	15
	oral	50 mg/kg	one	tissue degeneration, especially heart, liver, kidney	16
	oral	>1 mg/kg	one	lowered hemoglobin, erythrocytes and lymphocytes: increased leucocytes	17
	oral	0.1 mg/kg	one	threshold toxic dose	17
guinea pig	inhalation	saturated air (0.04 volume %)	2-5 hours	death following tremors, paralysis of hind legs	9
	inhalation		2-3 hours	death	9
	subcutaneous injection	0.2 gm/kg	every other day for 6 months	hemolytic anemia, loss of weight decreased motor activity, fluxes in urinary excretion of 17-oxo-corticosteroids	18

Organism	Route	Dose Concentration	Exposure Time	Response	Reference
guinea pig	oral	ca. 3 gm	one	0.5 hours: tremors, faint heart-beats, labored respiration 2 hours: death	9
	oral	ca. 1.2 gm	one	immediately motionless, then complete recovery	9
	oral	50 mg/kg	<1 year	tissue degeneration, especially heart, liver, kidney	17
	oral	>1 mg/kg	one	lowered hemoglobin, erythrocytes, lymphocytes; increased leucocytes	17
	oral	0.1 mg/kg	one	threshold toxic dose	17
rat	inhalation	5 mg/m^3	8 hours	metabolites excreted in 3 days	1
	inhalation	ca. 0.03 mg/m^3	daily, up to 98 days	increased ability to form sulfhemoglobin in preference to methemoglobin	19
	inhalation	0.06-0.1 mg/m^3	70-82 days	cerebellar disturbances, inflamed internal organs	20
	inhalation	0.008 mg/m^3	73 days	no effect	3
	oral	0.6 gm/kg	one	LD_{50}	21
	intraperitoneal injection	0.8 gm/kg	one	lethal	22

Organism	Route	Dose Concentration	Exposure Time	Response	Reference
rat	subcutaneous injection	640 mg/kg	one	blood catalase activity decreased continuously over 96 hours	23
	subcutaneous injection	300 mg/kg	one	LD 14 -methemoglobinemia anemia, sulfhemoglobinemia	G14
	subcutaneous injection	200 mg/kg or 100 mg/kg	one daily for 10 days	methemoglobinemia, sulfhemoglobinemia, anemia	25
	subcutaneous injection	125 mg/kg	one	delayed embryogenesis, abnormal fetal development and embryo death, changes in polysaccharide composition of placenta	26 27 28
	subcutaneous injection	100-200 mg/kg	one	sulfhemoglobin (most regular and persistent form of hemoglobin) nitroxyhemoglobin, increased methemoglobin	29
mouse	cutaneous absorption	480 gm/kg	-	30 min. - prostrate, motionless 24 hours - death	2
	intraperitoneal injection	1.23 gm/kg	one	40 min. - 67% dead	30
	intraperitoneal	1 gm/kg	one	10-15 min. - incoordination, comatose, shallow respiration several hours - regained coordination immediately before death - lost coordination again, respiratory arrest 48 hours - death	30

Organism	Route	Dose Concentration	Exposure Time	Response	Reference
mouse	intraperitoneal injection	20 mg/kg	one	lethal dose	24
	intraperitoneal injection	12.3 mg/kg	one	10 minutes: 4.2% methemoglogin formed	30
cat	inhalation	saturated air (volume %: 0.04)	2-5 hours	death following tremors, paralysis of hind legs	9
	inhalation	-	2-3 hours	death	
	oral	2.4 gm	one	death in 12 to 24 hours	2,9
dog	inhalation	"thick vapor"	1 1/2 hours	complete anesthesia and sleep	9
	intravenous injection	0.15-0.25 gm/kg	one	minimum lethal dose. lowered blood pressure, pulse rate increased then decreased, respiration stimulated until paralyzed	2
	oral	28.8 gm plus 6 gm	2 doses, 0.5 hours apart	immediate - agitation, then motionless 1 hour - convulsions, then motionless 4.5 hours - tremors, hind legs paralyzed 18 hours - death	9
	oral	24 gm	one	few hours - "stupid" (sic) 12 hours - deep coma, slow respiration, lowered skin temperature, stomach strongly alkaline	9

Organism	Route	Dose Concentration	Expsoure Time	Response	Reference
dog	oral	2.4 gm	one	1 hour - vomiting, then sleepy, continuing for 6 hours 6 hours - appears normal 15-81 hours - rigid muscles 104 hours - death	9
	oral	0.75-1.0 gm/kg	one	minumum lethal dose	2
	oral	0.5-0.7 gm/kg	one	salivation, unrest, dizziness, tremors, increased pulse rate, sometimes convulsions	9
	oral	-	daily	formed methemoglobin continuously at "certain" concentration	31
chicken	oral	1.2 gm	one	unsteady gait, recovery	9
	oral	2.4 gm	one	immediately unconscious	9
pigeon	inhalation	-	1 hour 2-3 hours	no effects death	9
frog	inhalation	saturated air (volume %: 0.04)	-	general depression	2,9
	oral, sub-cutaneous injection or inhalation	-	-	paralysis of all movement, abolition of all reflexes, death	9

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TOLUENE

TABLE OF CONTENTS

	Page
Overview	IX-1
Part I - General Information	IX-3
Specific References	IX-7
Part II - Biological Properties	
2.1 Bioaccumulation	IX-8
2.2 Contaminants and Environmental Degradation or Conversion Products	IX-8
2.3 Acute Toxicity	IX-9
2.4 Other Toxic Effects	IX-11
2.5 Carcinogenicity	IX-12
2.6 Mutagenicity	IX-13
2.7 Teratogenicity	IX-14
2.8 Metabolic Information	IX-14
2.9 Ecological Effects	IX-15
2.10 Current Testing	IX-17
References	IX-20

TOLUENE

AN OVERVIEW

Toluene is a clear, colorless, refractive, noncorrosive liquid with a sweet pungent odor similar to that of benzene. Toluene is quite stable in air, slightly soluble in water and miscible with alcohol, ether and benzene.

Toluene is produced in the U.S. primarily from petroleum; smaller quantities are produced from coal. Annual production is in excess of 5 billion pounds.

Toluene is widely used as a solvent, as a gasoline additive and has many other household and industrial uses; e.g., as an intermediate in the manufacture of trinitrotoluene (TNT), benzaldehyde and benzoic acid.

Toluene has an unusually high occupational exposure, estimated to involve more than 4 million workers. This ranks it as sixth in the NOHS survey of 7000 agents in the workplace. Release to the general environment occurs from evaporation of gasoline, in emissions from production facilities and from coke ovens. Toluene is currently being substituted for benzene in many uses and has an annual release rate exceeding 1 billion pounds. Both the occupational and general population exposures are large.

In man, toluene is metabolized primarily to benzoic acid, the major portion of which is conjugated with glycine in the liver and excreted almost entirely in the form of hippuric acid. No evidence of bioaccumulation of toluene has been found. Effects of toluene on fish, algae, bacteria, and other organisms have been reported only at levels far higher than those likely to occur in the environment.

Toluene is primarily a central nervous system depressant in both humans and animals. Evidence for hematopoietic or myelotoxic dysfunction is inconclusive. Carcinogenicity tests with toluene by skin applications have given positive or negative results of borderline significance. No information on the teratogenicity of toluene has been reported. Mutagenicity studies in humans exposed to toluene have been reported in Russian literature.

TOLUENE

PART I

GENERAL INFORMATION

1.1 Identification CAS No.: 000108883
NIOSH No.: XS52500

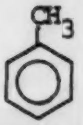
(G16)

1.2 Synonyms and Trade Names

Methylbenzene; toluol; phenylmethane; methacide

(G23)

1.3 Chemical Formula and Molecular Weight



C_7H_8 Mol. wt. 92.15 (G22,G23)

1.4 Chemical and Physical Properties

1.4.1 Description: Colorless liquid with benzene-like odor

(G23)

1.4.2 Boiling point: 110.6° C (G22)

1.4.3 Melting point: -95° C (G22)

1.4.4 Absorption Spectrometry:

$$\lambda_{max}^{alcohol} = 207, 260 \text{ nm};$$

$$\log \epsilon = 3.97, 2.48$$ (G22)

1.4.5 Vapor Pressure: 40 mm at 31.8° C (G22)

1.4.6 Solubility: Soluble in water 534.8 ppm;
Soluble in acetone, ligroin, carbon disulfide;
Soluble in all proportions in alcohol, benzene, ether

(G22)(1)

1.4.7 Octanol/Water Partition Coefficient:

$$\log P_{oct} = 2.69$$ (G36)

1.5 Production and Use

1.5.1 Production:

5,917.200	Million lbs	(1972)	
5,040.519	Million lbs	(1975)	
7,138.997	Million lbs	(1976)	(G24)

1.5 Production and Use (Continued)

1.5.2 Use: In aviation gasoline and high-octane blending stock; in manufacture of benzene, phenol and caprolactam; as a solvent for paints and coatings, gums, resins, most oils, rubber, vinyl organosols; as a diluent and thinner in nitrocellulose lacquers; as an adhesive solvent in plastic toys and model airplanes; in manufacture of chemicals (benzoic acid, benzyl and benzoyl derivatives); in manufacture of saccharin, medicines, dyes, perfumes, explosives (TNT); as a source of toluene diisocyanates (polyurethane resins); in toluene sulfonates (detergents); as a fluid in scintillation counters

(G21)

Quantitative Distribution of uses:

	Percent
Benzene	51
Solvents	10
Explosives	9
Isocyanates	5
Phenol	1
Gasoline pool and miscellaneous	24
	100

(G25)

Consumer Product Information:

Category	No. of toluene containing products	$\frac{\text{No. of Toluene products in category}}{\text{Total no. of products in category}} \times 100$
Household aerosols	1014	26.99%
Paints, varnishes, shellac, rust preventatives, etc.	272	2.47%
Adhesives and adhesive products including glue	61	11.55%
Paint and varnish thinners	20	62.50%
Flame-retardant chemicals	13	2.20%
Cleaning agents and compounds	5	0.28%
Solvent-based cleaning and sanitizing agents	3	1.38%
Paint and varnish remover	2	18.18%
Photographic chemicals	1	1.25%
Caustics, lyes and drain cleaners	1	0.44%
Other chemicals	1	1.55%

The 1,393 products surveyed contained an average of 12.2% toluene.

(G27)

Toluene is present in:

adhesives - model and china cement, construction adhesive
paint and varnish removers
stain removers and dry cleaners
nail polishes
inks- permanent markers
fuel system antifreeze
paints and paint thinner
asphalt remover
metal cleaner
anthelmintic - veterinary (G35)

1.6 Exposure Estimate

1.6.1 Release Rate: 1,074.2 Million lbs (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 6

Estimated no. of persons exposed: 4,811,000 (G29)

1.7 Manufacturers

From petroleum:

American Petrofina Co. of Texas
Ashland Oil Co.
Atlantic Richfield Co.
BP Oil Corp.
Champlin Petroleum Co.
Charter Oil Co.
Coastal States Marketing, Inc.
Commonwealth Petrochemicals Co.
Cosden Oil and Chemical Co.
Crown Central Petroleum Corp.
Exxon Corp
Gulf Oil Corp.
Marathon Oil Co.
Mobil Oil Corp.
Monsanto Co.
Phillips Petroleum Co.
Shell Chemical Co.
Southwestern Oil and Refining Co.
Standard Oil Co. of Calif.
Sun Oil Co. of Pa.
Suntide Refining Co.
Tenneco, Inc.
Texaco, Inc.
Union Oil Co. of Calif.

From Coal:

- Armco Steel Corp.
- Bethlehem Steel Corp.
- CF and I Steel Corp.
- Indiana Gas and Chemical Corp.
- Interlake, Inc.
- Jones and Laughlin Steel Corp.
- Mead Corp.
- Republic Steel Corp.
- United States Steel Corp.

By-Product Toluene:

- Dow Chemical USA
- Foster Grant Co., Inc.
- Monsanto Co.
- Union Carbide Corp.

(G25)

SPECIFIC REFERENCE FOR PART I

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TOLUENE

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

No report on the bioaccumulation of toluene could be found in the searched literature. Mammals are reported to metabolize about 80% of absorbed toluene and exhale about 20% (1). Toluene is oxidized to benzoic acid which is conjugated with glycine and excreted as the water-soluble hippuric acid. In an 18-hour experiment with humans, 68% of absorbed toluene was excreted as hippuric acid following exposure to 100 and 200 ppm toluene (2). Toluene has a high octanol/water partition coefficient ($\log P_{oct} = 2.69$), but its rapid metabolism would probably preclude bioaccumulation (3). Compounds with potential for significant bioaccumulation in organisms are reported to be those having water solubilities less than 50 ppm (4); toluene has a solubility of 534.8 ppm in distilled water (5).

2.2 Contaminants and Environmental Degradation or Conversion Products

Benzene is a common contaminant of toluene. Highly purified toluene (reagent grade and nitration grade) contains less than 0.01% benzene as contaminant. Industrial grade and cruder-grade toluene (90-120°C boiling range) contain significant quantities of benzene (as much as 25%) and probably other hydrocarbons as well (G19). Myelotoxic effects attributed to toluene on the basis of early studies are judged by more recent investigators to probably result from concurrent exposure to benzene present as a contaminant (G19). The possibility that bone marrow and other effects are attributable to contaminating benzene remains open.

In the atmosphere, toluene may be subject to photochemical degradation (6). Toluene exhibited moderate reactivity in studies conducted in smog chambers (6). However, its long-term stability under true atmospheric conditions remains unknown.

Some microorganisms can metabolize toluene (see Section 2.8).

2.3 Acute Toxicity

The NIOSH Registry of Toxic Effects of Chemical Substances (G16) reports the acute toxicity of toluene as follows:

Parameter	Dosage	Animal	Route	Reference
LD50	5000 mg/kg	rat	oral	7
LCLo	4000 ppm/4H	rat	inhalation	8
LDLo	800 mg/kg	rat	intraperitoneal	9
LDLo	5000 mg/kg	rat	subcutaneous	10
LD50	1640 mg/kg	rat	intraperitoneal	11
LC50	5300 ppm	mouse	inhalation	12
LD50	14 g/kg	rabbit	skin	13

Information on the purity of the toluene used in the above-listed tests has been reported only where it contained 0.01% benzene. For a

60% benzene and 40% toluene mixture the inhalation LC50 in mice was reported as 7200 ppm (12).

Toluene is a primary skin irritant. Contact of toluene with pulmonary tissue causes chemical pneumonitis, pulmonary edema and hemorrhage. It damages the cornea on contact. It is irritating to the mucous membranes of the respiratory tract. The degree of irritation depends on the concentration and the duration of the exposure (14).

Central nervous system depression, headache, giddiness, fainting, weakness, paresthesia, disturbance of coordination and equilibrium, and loss of consciousness are the symptoms of acute systemic toluene intoxication (14).

The effects observed (14) in human subjects exposed to toluene for an eight-hour period are summarized below:

Toluene in Air ppm	Signs and Symptoms
50	drowsiness, headache
100	fatigue, sleepiness
200	insomnia, incoordination, paresthesia, nausea, confusion, weakness
600	dizziness, staggering, lack of self control
800	severe nervousness, muscular fatigue and insomnia, which lasted for several days

Animal and human responses to the vapor inhalation of "50 thinner," a commercial solvent containing 32% toluene, 65% heptane, and 3% other hydrocarbons have been reported recently by Carpenter et al. (15) as follows:

Animal	Response
rats	LC50(4 hours) was 33 mg/liter (8300 ppm). Tolerated 5.2 mg/liter (1300 ppm) for 4 hours without any signs of discomfort.
dogs (beagles)	Tolerated 2.4 mg/liter (600 ppm) for 6 hours without any sign of discomfort (no ill effect level).
cats	At 30 mg/liter (7600 ppm) for 6 hours developed signs of central nervous system effects but survived.
human	During 15-minute inhalation periods the only irritative response was a mild sensation of dryness of the eyes in one of the five subjects inhaling 0.83 mg/liter (210 ppm) or 1.7 mg/liter (430 ppm). The same subject felt "light-headed" at 2.0 mg/liter level in both 15 and 30 minute inhalation periods. The concentration of 1.7 mg/liter (430 ppm) was suggested as the hygienic standard.

2.4 Other Toxic Effects

Continued or repeated skin contact with toluene will cause dermatitis due to dehydration and removal of the natural fats from the skin (14). The inhalation of toluene vapors may cause loss of appetite, nausea and vomiting and evidence of central nervous system effects (headache, fatigue, nervousness and insomnia). Pain in the chest, nosebleed, liver enlargement and intolerance to alcohol have been reported in man following repeated exposure to toluene (14).

The myelotoxic effect of toluene has been the subject of persistent controversy. Much of this controversy is attributable to the experimental use of toluene derived from coal tar which was contaminated to varying degrees with benzene (1, G19).

Studies in experimental animals show rather convincingly that toluene is not myelotoxic. In rabbits, subcutaneous injections of pure toluene did not result in depression of bone marrow function or changes in peripheral blood at doses of 300 mg/kg/day for six weeks or 700 mg/kg/day for nine weeks (16). No significant bone marrow toxicity or adverse effect on other organs was reported in a study of workers exposed to ambient toluene concentrations of 200-800 ppm (1). It has been reported that leukemia patients tolerated daily doses of 10 g toluene in olive oil for three weeks without complaints or clinical evidence of side effects (G19). Based on a large number of blood examinations of many persons exposed to toluene, no effect on the blood comparable to that of benzene has been observed except where the toluene was found to contain some benzene (G2).

The Threshold Limit Value (TLV) recommended by the ACGIH (1976) is 375 mg/m^3 (100 ppm) for skin exposure (G11).

2.5 Carcinogenicity

Skin application studies have given inconclusive results.

In one study (17), toluene was applied three times weekly to the skin of the intrascapular region for the lifetime of the mice. No evidence of the carcinogenicity of the compound was revealed.

Toluene (16-20 μl) was applied topically to the skin of 30 mice, twice weekly for 72 weeks. Tumors occurred in two mice and were diagnosed histologically as a skin carcinoma and a skin papilloma (18, as reported in G18).

Two other studies (G18) of the potential carcinogenicity of toluene gave negative results. However, they are of less significance due to the limited number of animals used, the short duration of the experiments, or both. In one study toluene was administered by subcutaneous injection, at a dose rate of 1 mg/kg body weight in olive oil, daily for up to 51 days (G18). In another study toluene was administered to an unspecified number of rats by stomach tube at doses of 118, 354, 590 mg/kg/day in olive oil (emulsified with 5-10% aqueous solution of acacia). Observations of the test animals for 193 days revealed no tumors (19).

2.6 Mutagenicity

Walker (1) has cited two Russian studies on the mutagenicity of toluene. Rats given toluene (1 mg/kg body weight) subcutaneously, daily for twelve days showed evidence of bone marrow chromosome damage (20). Subcutaneous administration of 0.8 g/kg to rats for 12 days was reported to have stimulated neutropoiesis and induced metaphase aberrations and chromosomal breaks in the laminar cells of bone marrow (21).

Chromosome studies were carried out on peripheral blood lymphocytes of 34 workers of a rotogravure plant and 34 controls matched for sex and age. Ten of the workers were exposed to benzene before 1953 and then to toluene and 24 have been exposed only to toluene after 1953. The frequencies of chromosome changes in the benzene group were higher than in the toluene group and the differences were statistically significant. The group of subjects exposed to toluene showed a higher rate of unstable chromosome changes and of calculated breaks compared to the controls, but the difference was not statistically significant (22).

Mutagenic effects of benzene, toluene and a mixture of benzene and toluene (1:2) by inhalation (4 hrs. daily for 4 months) have been recently reported (23) in an abstract of a Russian article as follows:

Test Material	Dosage mg/m^3	Percentage of metaphases with damaged chromosomes in bone marrow	Additional effects
Benzene	300	27.42	Leukocytopenia
Toluene	610	21.56	Leukosis
Benzene & Toluene	300 + 600	41.21	Leukosis
Controls	---	4.02	---

One month after the experiment the frequency of chromosome damage was still high, whereas the morphological composition of blood had almost completely returned to normal.

2.7 Teratogenicity

No information found in the searched literature.

2.8 Metabolic Information

The metabolism of toluene involves oxidation and conjugation prior to excretion. The following sequence represents the major pathway for the oxidation of toluene in mammalian systems (24).

$$\text{Toluene} \longrightarrow \longrightarrow \text{Benzyl alcohol} \longrightarrow \longrightarrow \text{Benzoic acid} \longrightarrow \longrightarrow \text{Hippuric acid}$$

In man and rabbits, toluene is oxidized in 80% yield to benzoic acid, the major portion of which is conjugated with glycine in the liver and excreted in the form of hippuric acid. The *in vivo* metabolism of toluene by rats has been shown to produce *o*- and *p*-cresol. Rabbit liver microsomes also oxidize toluene to small amounts of these phenols (24).

The microbial oxidation of toluene has been reported by several investigators. *Pseudomonas aeruginosa* oxidizes toluene through benzyl alcohol, benzaldehyde, benzoic acid and catechol (25). Claus and Walker (26) isolated strains of two bacteria (*Pseudomonas* and *Achromobacter*) which appeared to metabolize toluene via 3-methyl-catechol, according to the following sequence:

Toluene → → 3-methylcatechol → → Unidentified yellow ether-soluble acidic substance → → acetic acid and pyruvic acid

Initial reactions in the oxidation of toluene by *Pseudomonas putida* were reported (27) to form 2,3-dihydroxy-2,3-dihydrotoluene as an intermediate preceding formation of 3-methylcatechol. The non-enzymatic product of this intermediate is *o*-cresol.

Proposed reactions for the *in vivo* metabolism of toluene in mammalian systems and initial reactions in the oxidation of toluene by *Pseudomonas putida* as reported in the literature (24, 27) are shown in Figures 1 and 2, respectively.

2.9 Ecological Effects

Total annual emissions of toluene to the environment have been estimated to be about 450,000 metric tons (G28) with 99.3% of this amount going to the atmosphere and 0.7% to waste water. Toluene concentrations in grab and composite samples of industrial water effluents have been found to range from 0.04 to 0.28 ppm (28). Influent water from the two Ohio municipal wastewater treatment plants contained from 8 to 150 ppb toluene in 13 of 15 samples and 1 to 10 ppb toluene in 4 of 11 samples in which toluene was detected (29). Toluene is volatile and is readily transferred from water surfaces to the atmosphere (30). In Los Angeles, toluene concentration in air was 37 ppb on the average and 129 ppb maximum (31); in Toronto, the average concentration in the summer of 1970 was 30 ppb and 188 ppb maximum (32). The presence of toluene in the atmosphere is said to be attributable primarily to auto emissions (31).

Effects of toluene exposure on humans and animals (rats, mice, guinea pigs, dogs, and rabbits), mostly by inhalation, are summarized in Sections 2.3 and 2.4. Toxic effects have been reported only at levels greatly in excess of those encountered in the ambient atmosphere.

In a continuous flow bioassay study, LD50s for goldfish (Carassius) were determined to be 42 ppm and 23 ppm for 24 and 96 hours, respectively. Fish were exposed to toluene emitted from outboard motor exhausts in this experiment (33). Toxicity of toluene to the fathead minnow, bluegill, goldfish, guppy, and orange-spotted sunfish has been reported. LC50 values all exceeded 24 ppm in exposures of 24- to 96-hours duration (34, 35).

The Aquatic Toxicity Rating (96 hr. TLm, species unspecified) of toluene is 100-10 ppm (G16).

Tests of four pseudomonads (motile marine bacteria) at toluene concentrations of 0.1 and 0.5% showed strong negative chemotactic responses (movement away from high concentrations of the chemical) (36). Toluene at a concentration of 0.6% inhibited the normal positive chemotactic response of marine bacteria to glucose in seawater (37).

Studies of the effect of toluene on the growth of the unicellular green alga Chlorella vulgaris showed an LC50 of 245 ppm. Toxicity thresholds of 10^4 mg/l for the algae Skeletonema costatum, Amphidinum carterae and Cricrosphaera carterae, and 10^5 mg/l for Dunaliella tertiolecta have been reported (38).

Toluene is a contact poison in terrestrial plants at very high concentrations (greater than 5,000 ppm). At ambient atmospheric levels, however, toluene has not been shown to have any adverse effects (39).

The transport and fate of toluene within organisms is not well known. A variety of pure cultures of microorganisms have been shown to have enzymatic systems capable of metabolizing toluene (24, 26, 40).

2.10 Current Testing

Toluene has been designated by the Chemical Industry Institute of Toxicology (CIIT) for investigation of toxic and carcinogenic effects following chronic inhalation exposure in at least one mammalian species. A summary report is available on a 90-day inhalation study in albino rats. The study, conducted by Industrial Biotest Laboratories for CIIT, involved commercial toluene containing 100 ppm benzene.

The study was conducted with 4 groups of 30 animals exposed to either 30, 100, 300 or 1000 ppm. An additional group of 30 rats served as an untreated control. Observations were made of mortality, reactions displayed, food consumption, body weight, hematologic and clinical chemistry. The only mortalities recorded throughout the investigation occurred during blood collection.

Effects in male rats were limited to red deposits and/or red discharge around the nose, and red deposits around the eyes. The only effect noted in female rats was alopecia around the ears. No significant differences between control and test animals were reported in body weight, hematologic or clinical chemistry, urinalyses, or the frequency of histopathologic changes.

Figure 1. Proposed reactions for the *in vivo* metabolism of toluene (24).

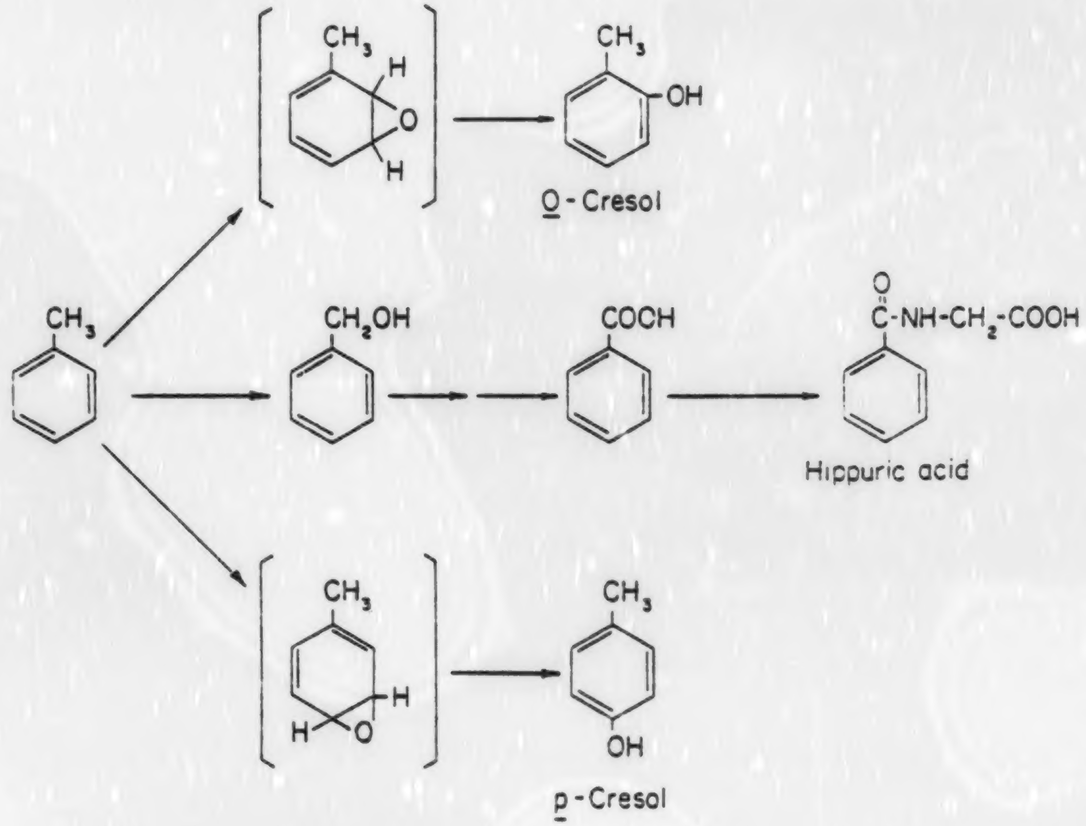
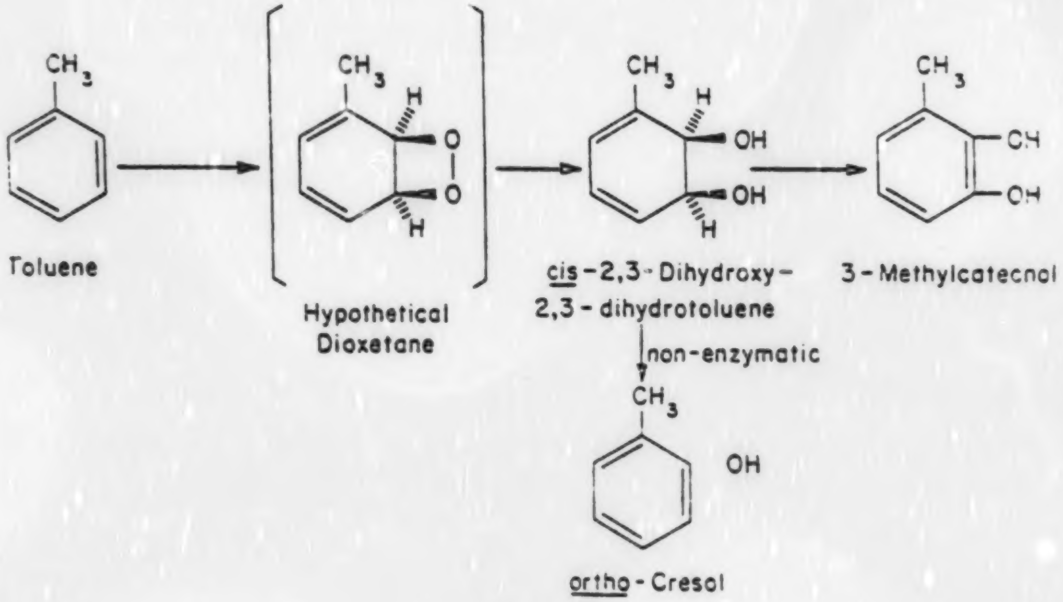

CH3
H
O
H
CH3
OH
O-Cresol
CH3
CH2OH
COOH
O
C-NH-CH2-COOH
Hippuric acid
CH3
H
H
O
CH3
OH
p-Cresol

Figure 2. Initial reactions in the oxidation of toluene by *Pseudomonas putida* (24).


CH3
Toluene
CH3
H
O
O
H
Hypothetical
Dioxetane
CH3
H
OH
OH
H
cis-2,3-Dihydroxy-
2,3-dihydrotoluene
non-enzymatic
CH3
OH
ortho-Cresol
CH3
OH
OH
3-Methylcatechol

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XYLENES

TABLE OF CONTENTS

Page

Overview X-1

Part I - General Information

Xylenes, mixed X-3

m-Xylene X-6

o-Xylene X-8

p-Xylene X-10

Summary of Characteristics X-12

Specific References X-13

Part II - Biological Properties

2.1 Bioaccumulation X-14

2.2 Contaminants and Environmental Degradation or Conversion Products X-14

2.3 Acute Toxicity X-15

2.4 Other Toxic Effects X-18

2.5 Carcinogenicity X-23

2.6 Mutagenicity X-23

2.7 Teratogenicity X-23

2.8 Metabolic Information X-24

2.9 Ecological Effects X-27

2.10 Current Testing X-27

References X-28

XYLENES

AN OVERVIEW

There are three isomers of xylene: o-xylene, m-xylene, and p-xylene. All three isomers, as well as mixtures, are articles of commerce. In this dossier, "xylene" refers to a mixture of the three isomers, unless otherwise stated. o-, and m-Xylene are colorless liquids; p-xylene is a crystalline solid melting at 13°C. Xylenes are insoluble in water but miscible with alcohol, ether and many organic solvents.

Commercial xylene which is predominantly the m-isomer is produced both from petroleum and from coal tar. o- and p-Xylene, ethylbenzene, and small quantities of other aromatic hydrocarbons are also present in the commercial product. In the aggregate, approximately 10 billion pounds of xylene are produced annually.

Xylene is used by industry as a raw material for the production of several chemicals, and as a solvent, having replaced the more toxic benzene for a number of solvent uses. In the NOHS survey of occupational exposure, xylene (mixed isomers) was ranked 13th out of approximately 7000 agents: more than 4 million workers are believed to be exposed to it. Its presence in a wide variety of consumer products results in general population exposures as well. Approximately 900 million pounds are released to the environment each year.

Xylenes are expected to bioaccumulate appreciably, as a result of their partitioning into organic solvents, and storage in fish and shellfish has been reported. No reports of ecological damage have been attributed to xylenes. However, low levels cause tainting in fish and shellfish. Xylene isomers are oxidized to o-, m- and p-toluic acids, which are excreted as water-soluble conjugates. Xylenols also form as minor metabolites. Bacteria oxidize xylenes to dihydrodiols, catechols, and xylenols.

Toxic effects in humans following acute and/or chronic exposure to xylene include narcosis, liver, kidney and heart damage. When contaminated with benzene, commercial xylene has been reported to be myelotoxic. Animal data on the carcinogenicity of xylenes are not adequate for an evaluation, and xylenes have been tentatively selected for carcinogenicity testing by NCI. Mutagenicity tests have not been reported for any of the xylenes. According to Russian studies, xylenes are embryotoxic.

XYLENES

PART I

GENERAL INFORMATION

I. Xylenes, mixed

1.1 Identification CAS No.: 001330207
NIOSH No.: ZE21000

1.2 Synonyms and Trade Names

Dimethylbenzene; xylol (G16)

1.3 Technical Product Composition

20% o-xylene
40% m-xylene
20% p-xylene
20% ethylbenzene
small quantities of toluene and C_9 aromatics (1)

1.4 Chemical and Physical Properties

1.4.1 Description: Clear, mobile, flammable liquid (G21,G23)

1.4.2 Boiling Point: 137 - 140° C (G23)

1.4.3 Melting Point:

No information found in sources searched

1.4.4 Absorption Spectrometry:

No information found in sources searched

1.4.5 Vapor Pressure:

No information found in sources searched

1.4.6 Solubility: Insoluble in water; Soluble in alcohol, ether and other organic liquids (G21,G23)

1.4.7 Octanol/Water Partition Coefficient:

$\log P_{oct} = 3.13$ (estimate) (G36)

1.5 Production and Use

1.5.1 Production:

5,336	Million lbs	(1972)
5,666	Million lbs	(1973)
5,821	Million lbs	(1974)
4,608	Million lbs	(1975)

(2)

1.5.2 Use:

In aviation gasoline: in protective coatings: as a solvent for alkyl resins, lacquers, enamels, rubber cements: in synthesis of organic chemicals

(G21)

Quantitative Distribution of Uses:

	Percent
p-Xylene	39
o-Xylene	18
Other isomers for chemical use	6
Gasoline, benzene, solvent, and miscellaneous uses	37
	100

(G25)

Consumer Product Information:

Category	No. of mixed xylene containing products	$\frac{\text{No. of mixed xylene products in category}}{\text{total no. of products in category}} \times 100$
cleaning agents and compounds	1	0.05%
paints, varnishes, shellac, rust preventatives, etc.	477	4.3%
flame retardant chemicals	15	2.5%
household aerosols	579	15.4%
solvent-based cleaning and sanitizing agents	7	3.2%
caustics, lyes and drain cleaner	2	0.9%
agricultural chemicals	1	1.4%
adhesives & adhesive products including glue	4	0.8%
caulking & spackle	6	9.2%
paint & varnish thinners	3	9.4%

The 1,095 products surveyed contained an average of 9.5% mixed xylene.

(G27)

Xylene is present in:

Fuel system cleaner
Automatic choke and carburetor cleaner
Bullet and chisel point markers - permanent
Pigmented ink
Permanent ink
Water repellent wood preservative
Penetrating solvent
Nail enamels
Liquid transmission additive
Spray paint
On and below grade adhesive
Marine paint
Edge dye for shoe soles
Laundry tub and appliance finish
Spot remover
Miticide (G35)

1.6 Exposure Estimates

1.6.1 Release Rate: 904.6 Million lbs (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 13

Estimated no. of persons exposed: 4,304,000 (G29)

1.7 Manufacturers

American Oil Co.
American Petrofina Co. of Texas
Ashland Oil, Inc.
Atlantic Richfield Co.
Crown Central Petroleum Corp.
Commonwealth Petrochemicals, Inc.
Cosden Oil and Chemical Corp.
Cities Service Oil Co.
Exxon Chemical Co.
Gulf Oil Corp., Gulf Oil Chemicals Co.
Champlin Petroleum Co.
Hercor Chemical Corp.
Amerada Hess Corp.
Marathon Oil Co., Texas Refining Div.
Monsanto Co.
Phillips Puerto Rico Core, Inc.
Shell Oil Co., Shell Chemical Co. Div.
Standard Oil Co. of California, Chevron Chemical Co.
Charter International Oil Co.
Styrochem Corp.
Sun Oil Co.
Tenneco Oil Co.
Union Carbide Corp.
Union Oil Co. of California

(G24)

XYLENES

II. *m*-Xylene

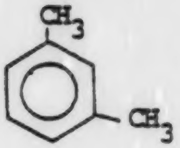
1.1 Identification

CAS No.: 000108383
NIOSH No.: ZE22750

1.2 Synonyms and Trade Names

1,3-Dimethylbenzene; *m*-xylol (G16)

1.3 Chemical Formula and Molecular Weight



C_8H_{10} Mol. Wt. 106.17

(G22)

1.4 Chemical and Physical Properties

1.4.1 Description: Clear, colorless liquid (G21)

1.4.2 Boiling Point: 139.1° C (G22)

1.4.3 Melting Point: -47.87° C (G22)

1.4.4 Absorption Spectrometry:

$$\lambda_{max}^{cyclohexane} = 269,\ 274\ \text{nm};$$

$$\log \epsilon = 2.3,\ 2.3$$ (G22)

1.4.5 Vapor Pressure: 10 mm at 28.3° C (G22)

1.4.6 Solubility: Insoluble in water;
Soluble in all proportions in alcohol, ether, acetone, benzene, petroleum ether and other organic solvents (G22)

1.4.7 Octanol/Water Partition Coefficient:

$$\log P_{oct} = 3.20$$ (G36)

1.5 Production and Use

1.5.1 Production: 1,710 Million lbs (G15)

1.5.2 Use: As a solvent; as an intermediate for dyes and organic synthesis, especially isophthalic acid; in insecticides; in aviation fuel (G21)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure:

Rank: 4284

Estimated no. of persons exposed: 2,000*

*rough estimate (G29)

1.7 Manufacturer

Atlantic Richfield Co. (G25)

XYLENES

III. o-Xylene

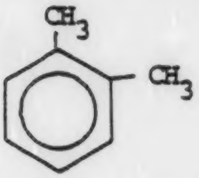
1.1 Identification

CAS No.: 000094576
NIOSH No.: ZE24500

1.2 Synonyms and Trade Names

1,2-Dimethylbenzene (G16)

1.3 Chemical Formula and Molecular Weight



C_8H_{10} Mol. wt. 106.17

(G22)

1.4 Chemical and Physical Properties

1.4.1 **Description:** Clear, colorless liquid (G21)

1.4.2 **Boiling Point:** 144.4° C (G22)

1.4.3 **Melting Point:** -25.18° C (G22)

1.4.4 **Absorption Spectrometry:**

$$\lambda_{max}^{cyclohexane} = 265, 271 \text{ nm};$$

$$\log \epsilon = 2.3, 2.2$$

(G22)

1.4.5 **Vapor Pressure:** 10 mm at 32.1° C (G22)

1.4.6 **Solubility:** Insoluble in water; Soluble in all proportions in alcohol, ether, acetone, benzene, carbon tetrachloride, and petroleum ether (G22)

1.4.7 **Octanol/Water Partition Coefficient:**

$$\log P_{oct} = 2.77$$

(G36)

1.5 Production and Use

1.5.1 Production: 702.923 Million lbs (1975)
853.813 Million lbs (1976) (G24)

1.5.2 Use: Current production is used almost entirely for the manufacture of phthalic anhydride which is employed in the production of alkyd resins, certain unsaturated polyester resins and plasticizers for polyvinyl chloride resins; also in vitamin and pharmaceutical synthesis; in dyes; in insecticides; in motor fuels

(G21,3)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure:

Rank: 3710

Estimated no. of persons exposed: 3,000*

*rough estimate (G29)

1.7 Manufacturers

Atlantic Richfield Co.
Chevron Chemical Co.
Cities Service Co.
Commonwealth Petrochemicals Co.
Cosden Oil and Chemical Co.
Crown Central Petroleum Corp.
Exxon Corp.
Monsanto Co.
Phillips Petroleum Co.
Shell Chemical Co.
Southwestern Oil and Refining Co.
Sun Oil Co.
Tenneco, Inc.

(G25)

XYLENES

IV. p-Xylene

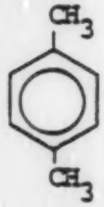
1.1 Identification

CAS No.: 000106423
NIOSH No.: ZE26250

1.2 Synonyms and Trade Names

1,4-Dimethylbenzene, p-xylol (G16)

1.3 Chemical Formula and Molecular Weight



C_8H_{10} Mol. wt. 106.17

(G22)

1.4 Chemical and Physical Properties

1.4.1 **Description:** Monoclinic prismatic crystals at low temperatures; colorless liquid (G21,G22)

1.4.2 **Boiling Point:** 138.35° C (G22)

1.4.3 **Melting Point:** 13.26° C (G22)

1.4.4 **Absorption Spectrometry:**

$$\lambda_{max}^{alcohol} = 267,\ 275\ \text{nm};$$

$$\log \epsilon = 2.7,\ 2.7$$

(G22)

1.4.5 **Vapor Pressure:** 10 mm at 27.3° C (G22)

1.4.6 **Solubility:** Insoluble in water;
Soluble in all proportions in alcohol, ether, acetone, benzene, petroleum ether and other organic solvents

1.4.7 **Octanol/Water Partition Coefficient:**

$$\log P_{oct} = 3.15$$

(G36)

1.5 Production and Use

1.5.1 Production:	2,483.521 Million lbs	(1975)	
	2,911.451 Million lbs	(1976)	(G24)

1.5.2 Use: In synthesis of terephthalic acid for polyester resins and fibers ("Dacron", "Mylar". "Terylene"); in vitamin and pharmaceutical synthesis; in insecticides

(G21)

1.6 Exposure Estimates

1.6.1 Release Rate: 39.9 Million lbs (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 3743

Estimated no. of persons exposed: 3,000*

*rough estimate (G29)

1.7 Manufacturers

Amoco Chemicals Corp.
Atlantic Richfield Co.
Charter Oil Co.
Chevron Chemical Co.
Cities Service Co.
Exxon Corp.
Harcor Chemical Corp.
Phillips Petroleum Co.
Shell Chemical Co.
Sun Oil Co.
Tenneco, Inc.

(G25)

SUMMARY OF CHARACTERISTICS
XYLENES

Name	Solubility	Log P_{oct}	Estimated Environmental Release (Million lbs)	Production (Million lbs)	Estimated no. of persons exposed (Occupational)	Use
Xylenes, mixed	i in H_2O; s in alc, eth, and other os	3.13	904.6	5,336 (1972) 5,666 (1973) 5,821 (1974) 4,608 (1975)	4,304,000	Synthesis of organic chemicals; aviation gasoline; protective coatings; solvent for alkyd resins, lacquers, enamels, rubber cements
m-Xylene	i in H_2O; ∞ in alc, eth, ace, bz, peth, and other os	3.20	*	~ 1,710 (1975)	~ 2,000	Solvent; intermediate for dyes and organic synthesis especially isophthalic acid; insecticides; aviation fuel
o-Xylene	i in H_2O; ∞ in alc, eth, ace, bz, peth and CCl_4	2.77	*	702.923 (1975) 853.813 (1976)	~ 3,000	Mfg. of phthalic anhydride; vitamin and pharmaceutical synthesis; dyes; insecticides; motor fuels
p-Xylene	i in H_2O; ∞ in alc, eth, ace, bz, peth and other os	3.15	39.9	2,483.521 (1975) 2,911.451 (1976)	~ 3,000	Synthesis of terephthalic acid for polyester resins and fibers; vitamin and pharmaceutical synthesis; insecticides

* No information found in sources searched.

SPECIFIC REFERENCES FOR PART I

1. Activities of the Chemical Selection Working Group, January-March 1977. Report to the Chemical Selection Subgroup of the Clearinghouse on Environmental Carcinogens, National Cancer Institute (18 April, 1977).

2. Summary of data for chemical selection - mixed xylenes. Stanford Research Institute, Menlo Park, California (1977).

3. Chemical and Engineering News (November 7, 1977).

XYLENES

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

Because of their high partition coefficients (log $P_{oct} \approx 3$) all isomers of xylene are expected to show a strong partitioning into the n-octanol phase of the n-octanol/water system. The retention of xylenes in organisms, however, is probably dependent on their metabolic fate, since the methyl groups of xylenes would tend to be readily oxidized, especially in mammalian systems. Evidence exists that eels may not have as much oxidizing capability, since xylenes do show some storage in eel tissues (2). While quantification was apparently performed, exact figures were not available at the time of this writing. All three isomers of xylene were stored at lower levels than either benzene or toluene in the eels' flesh. Fish from a polluted river in Japan were found to contain 0.02 ppm unspecified xylene in the flesh. Concentrations of both toluene and benzene in the same fish were roughly ten times as high. Concentrations in the water were not reported (3). Xylenes are also reported as being stored at unspecified levels in scallops from polluted waters (4).

In mammals, xylene was identified in rat brain tissue at unspecified concentrations and considered to be endogenous (5).

2.2 Contaminants and Environmental Degradation or Conversion Products

Commercial xylene is produced from petroleum and from coal tar. It generally has the following composition (G19).

Constituent	Petroleum Product	Coal Tar Product
o-Xylene	20%	10-15%
m-Xylene	44%	45-70%
p-Xylene	20%	23%
Ethylbenzene	15%	6-10%

Commercial xylene may also contain small amounts of toluene, trimethylbenzene, phenol, thiophene, pyridine and nonaromatic hydrocarbons. Xylene has frequently been contaminated with benzene (G19).

Xylenes have been reported in air (0.016 - 0.061 ppm for m-isomer; less for other isomers) (G14). The reactivity of xylenes to oxidation is low with estimated half-lives of 2200 years to peroxy radical and 100 years to ozone; the half-life for reaction with hydroxyl radical was reported to be 3 days (G14).

Products of microbial degradation (as in soil) are reported to be α-hydroxy-p-toluic acid, p-methylbenzyl alcohol, benzyl alcohol, m- and p-toluic acids and 4-methylcatechol (G14).

2.3 Acute Toxicity

Two publications, *Criteria for a Recommended Standard for Occupational Exposure to Xylene* by NIOSH (G19) and *Toxicity and Metabolism of Industrial Solvents* (G1), have served as the major secondary sources for the toxicity data and references cited in this and the following section (2.3 and 2.4).

Through the 1940s several papers appeared concerning occupational disease in the printing industry resulting from exposure to xylene. The relevance of these papers is questionable, however, as the term "xylene" is not precisely defined. "Xylene" as used in the intaglio printing industry might refer to pure xylene, pure toluene, a mixture of these, or a mixture containing benzene and paraffin hydrocarbons.

The NIOSH *Registry of Toxic Effects of Chemical Substances* (G16) reports the acute toxicity of xylene and individual isomers as follows:

Substance	Parameter	Dosage	Animal	Route
Xylene (mixed)	TCLo	200 ppm	human	inhalation
	LD50*	4300 mg/kg	rat	oral
	LDLo	2000 mg/kg	rat	intraperitoneal
m-Xylene	LD50	5000 mg/kg	rat	oral
	LCLo	8000 ppm/4H	rat	inhalation
	LDLo	2000 mg/kg	rat	intraperitoneal
	LDLo	5000 mg/kg	rat	subcutaneous
o-Xylene	LDLo	5000 mg/kg	rat	oral
	LDLo	1500 mg/kg	rat	intraperitoneal
	LDLo	2500 mg/kg	rat	subcutaneous
	LCLo	6920 ppm	mouse	inhalation
p-Xylene	LD50	5000 mg/kg	rat	oral
	LDLo	2000 mg/kg	rat	intraperitoneal
	LDLo	5000 mg/kg	rat	subcutaneous
	LCLo	3460 ppm	mouse	inhalation

* In this study by Wolf *et al*. (30) the material used was pure xylene (19% *o*-, 52% *m*-, and 24% *p*-). This is the only study in which purity and/or composition are reported.

According to the NIOSH Criteria Document, the only well-documented toxic effects of xylene in humans are its irritating and narcotizing properties (G19).

Liquid xylene is a skin irritant, causing erythema, dryness and defatting, and with prolonged contact, blistering. It is also an irritant to mucous membranes, including the conjunctiva and respiratory tract (G1, G19). Nelson *et al*. (31) found that xylene was more irritating than toluene to the eyes and mucous membranes during a 3 to 5 minute exposure. Narcotic inhalation doses reported by Browning (G1) in a review of literature prior to 1935 are: 2100 to 3500 ppm for the *m*- and *p*-isomers and 3500 to 10,000 ppm for *o*-xylene. Narcosis occurred only with concentrations higher than 1150 ppm. Xylene was reported in an article (32) cited by Browning (G1) to be slower in exerting an initial narcotic effect than either toluene or benzene at 15,000 ppm.

Narcotic effects in rats were noted at concentrations of 15-20 mg/l (3450-4600 ppm) for o-xylene, 10-15 mg/l (2300-3450 ppm) for m-xylene, and 10 mg/l (2300 ppm) for p-xylene (33, as reported in G19).

Carpenter et al. (34) investigated animal and human responses to vapors of mixed xylenes. The composition of the xylene used, as determined by gas chromatography, is shown in Table 1. It should be noted that no benzene was present in the sample.

TABLE 1 *

Composition of Mixed Xylenes

Components	Volume Percentage	
Nonaromatics	0.07	
Toluene	0.14	
Ethylbenzene	19.27	
p-Xylene	7.84	
m-Xylene	65.01	
o-Xylene	7.63	
C_9 + aromatics	0.04	
	100.00	Total

In this study, one of seven human volunteers exposed to 1.0 mg/l (230 ppm) and 1 of 6 exposed to 2.0 mg/l (460 ppm) experienced slight light-headedness without loss of equilibrium or coordination at the end of the 15-minute exposure period. In a 15-minute inhalation period, the only common sign of discomfort at 2.0 mg/l (460 ppm) was eye irritation, and some transitory olfactory fatigue (with recovery in 10 minutes) in four of six human test panel members. The authors concluded that the odor threshold is on the order of 0.0045 mg/l (1 ppm) and that 1.0 mg/l (230 ppm) of mixed xylenes should not be objectionable to most people, based on the following human sensory thresholds for mixed xylenes:

* From Carpenter et al. (38).

TABLE 2

Human Sensory Thresholds for Mixed Xylenes

Measured concentration mg/l	0.46	1.0	2.0	3.0
Measured concentration ppm	110	230	460	690
Number of volunteers	6	7	6	6
Number detecting odor	6	7	6	6
Number olfactory fatigue	3	3	3	0
Number throat irritation	1	0	1	2
Number eye irritation	0	1	4	4
Number with tears	0	1	1	2
Number reporting dizziness	0	1	1	4

The results obtained with animals in this same study are summarized below:

Rats inhaled 46 mg/l (11,000 ppm) of mixed xylenes. The LT50 was 92 minutes. The LC50 in a 4-hour inhalation period was 29 mg/l (6700 ppm).

Cats displayed central nervous system effects within 2 hours at 41 mg/l (9500 ppm).

Rats and beagles that inhaled 3.5 mg/l (810 ppm), 2.0 mg/l (460 ppm), and 0.77 mg/l (180 ppm) for 6 hours a day, 5 days a week for 13 weeks did not show differences (body weight change, urine and blood analysis) which were statistically significant from control groups.

Higher levels were not run because rats had poor coordination and dogs had lacrimation at 5-6 mg/l during a preliminary 4-hour exposure.

2.4 Other Toxic Effects

Rats and rabbits receiving 609 ppm and 1150 ppm xylene respectively, 8 hours a day, 6 days a week, for periods of 40-130 days showed some somnolence, and in the terminal phase dyspnea, disequilibrium and in some cases paralysis of the hind legs. At the higher concentrations, there was conjunctival irritation, anorexia and loss of weight at the end of the first week. Narcosis was more complete and prolonged. Ataxia, developing into paralysis of the hind legs with chattering of the teeth and redness of the mucous membranes, and hypothermia were also observed. At the similar dose, lesions in the kidneys, in the form of congestion, inflammation and cellular desquamation with some sign of commencing necrosis were observed in the animals (rats and rabbits) studied by Fabre et al. (35, as reported in G1). Liver necrosis and diffuse nephritis after xylene was injected intraperitoneally to rats, and moderate cloudy swelling of kidneys following exposure by inhalation have been reported (G1, G19).

Xylene is a central nervous system depressant. At high concentrations, brief exposures can affect attention, judgment, or perception (G19). Liver and kidney damage have been reported in a human after the inhalation of xylene and liver damage after the accidental ingestion of a small amount of a xylene-toluene thinner. In summary, effects of xylene have been reported on the liver (38), (37,39, as reported in G19); the kidney (38), (40, as reported in G19); the cardiovascular system (41, 42, as reported in G19); and the gastrointestinal tract (43, as reported in G19) after inhalation of xylene vapor. According to the NIOSH Criteria Document, effects on these organs and systems should be investigated to confirm or deny any involvement of xylene (G19).

The Threshold Limit Value (TLV) recommended by the ACGIH (1976) is 100 ppm (G11).

In the past, xylene has been considered myelotoxic because leukopenia, relative lymphocytosis and aplastic anemia were observed in occupational exposures, and transitory leukopenia, leukocytosis and hyperplasia of the bone marrow were reported in experimental animals. But in the NIOSH Criteria Document (G19), it is concluded that xylene is not myelotoxic when uncontaminated with substances such as benzene. This conclusion is based on the recent animal studies (34,36) in which exposure to pure xylene did not produce significant hematologic changes in rats, dogs, guinea pigs, or monkeys, while benzene has been reported to induce aplasia in other animal studies.

The major toxicity data summarized in the NIOSH Criteria Document (G19) have been compiled in Table 3.

TABLE 3

TOXICITY DATA ON XYLENES

Substance	Animal	Route	Dosage	Exposure Time	Effects	Reference
xylene	human	inhalation	200 ppm	3-5 min.	Irritation of eyes, nose, throat	44
Xylene	human	inhalation	10,000 ppm (estimated after the incident)	18.5 hrs.	3 painters in confined tank became unconscious, 1 died. Autopsy revealed severe lung congestion, focal intra-alveolar hemorrhage, pulmonary edema petechial hemorrhage in the brain and evidence of anoxic neuronal damage. Survivors suffered confusion, impaired renal function and hepatic impairment for about 1 month.	38
m-xylene	guinea pig	inhalation	300 ppm	4 hrs/day 6 weeks 6 da/week	Slight degeneration of the liver; inflammation of the lungs. At initial 450 ppm concentration one of the three animals died, others were prostrate.	45
p-xylene	pregnant rats	inhalation	115 ppm	24 hrs/day 20 days	Significantly greater pre-implantation mortality (32.1%) than controls (11.3%); significantly greater post-implantation mortality (38.9% vs 4.8%). No teratogenic effects.	11
xylene	chinchilla rabbits	inhalation	12 ppm	4 hrs/day for 10=12 months	Increases in hemoglobin, erythrocytes, leukocytes, common proteins, gamma globulin, increased activity of blood acetyl cholinesterase.	46

TABLE 3 - continued

Substance	Animal	Route	Dosage	Exposure Time	Effects	Reference
xylene (con't)					Decreases in weight, immunobiological activity, weakening of adrenal cortex functions, disturbance of intermediary metabolism.	
xylene	rat	inhalation	1600 ppm	18-20 hrs per day 2-4 days	Of original 4 rats, 1 died after two days, 1 after four days. Death was caused by narcosis which prevented ingestion of food and water leading to anhydremia and death. White cell count reduced 27% in one rat.	17
xylene	rat	inhalation	980 ppm	7 days	Effects similar to above without narcosis. Bone marrow and spleen were hyperplastic and kidneys showed acute congestion with moderate cloudy swelling.	17
xylene	rat	inhalation	620 ppm	7 days	30% reduction in white cells in 1 of 6 rats. No other toxic effects.	17
xylene	rat	subcutaneous	1-2 cc/kg 1:1 with olive oil	10 days	Slight reduction in activity and in the red cell count. Bone marrow became hyperplastic with mild necrosis of the liver and diffuse nephritis.	17
xylene	rabbits	inhalation	1150 ppm	8 hrs/day 6 da/wk 40-55 days	Decreases in red and white cells, hyperplastic bone marrow, no aplasia vascular congestion in the liver, heart, kidneys, adrenals, lungs, and spleen.	1

TABLE 3 - continued

Substance	Animal	Route	Dosage	Exposure Time	Effects	Reference
xylene (con't)						
	rabbits and rats	inhalation	690 ppm	8 hrs/day 6 da/wk 110-130 days	Same as in the 1150 ppm section except that there were no significant changes in the blood at this level.Renal lesions (glomerulonephritis) were observed at both dosage levels. (authors suggested that such effects in man would be indicated by an increase in blood urea and the appearance of albumin and blood in the urine and thus caution should be exercised in the use of xylenes)	1
xylene	rabbit	subcutaneous	300 mg/kg per day	6 weeks	Using radiographic techniques, it was determined that xylene does not affect DNA synthesis in the bone marrow. Earlier reports of aplastic anemia were probably due to benzene impurities	47
	rabbit	subcutaneous	700 mg/kg per day	9 weeks		
o-xylene	rats, guinea pigs, monkeys, dogs	inhalation	770 ppm	8 hrs/day 5 da/wk 6 weeks	Microscopic examination of heart, lung, brain, kidney, spinal cord and spleen were negative. No significant changes in body weight or leukocyte counts.	36
	rats, guinea pigs monkeys, dogs	inhalation	78 ppm	90 days continuous	same as above	
65% m-xylene 19.3% ethyl benzene 14.5% other xylenes	rats	inhalation	805 ppm 460 ppm 175 ppm	6 hrs/day 5 da/wk 13 weeks	No gross or microsopic lesions found. Blood counts and blood analyses were normal.	34

2.5 Carcinogenicity

Carcinogenicity testing of the xylenes by mouse skin painting has been reported (G18). In two studies (7, 8) of short duration (6-9 months) no malignant tumors were reported. These studies are not considered adequate for an evaluation of carcinogenicity because of the short duration, and the lack of data on dose levels and survival. In another mouse skin painting study, the activity of mixed xylenes could not be evaluated because of concurrent treatment with a single application of urethane followed by repeated applications of croton oil (10).

2.6 Mutagenicity

No reports on mutagenicity testing were found in the searched literature.

2.7 Teratogenicity

A Russian study (11) cited in the NIOSH Criteria Document (G19) examined the embryotoxic and teratogenic effects of p-xylene vapor. Rats were exposed to p-xylene at 115 ppm for 20 days, 24 hours per day. Treated rats experienced significantly greater pre-implantation mortality (32.1%) than controls (11.38%). Post-implantation mortality was also higher (38.9% vs. 4.8%). No teratogenic effects were observed. The conclusion was drawn by the author that p-xylene is much more toxic for the maternal organism than for the developing embryos.

A conclusion that fat solvents, including xylene, may have a teratogenic effect in man has been reported in a paper (12) cited in the NIOSH document. However, NIOSH makes clear that the data are not adequate to support the conclusions drawn by the authors of the article. The article reports that 9 spinal malformations (sacrococcygeal agenesis, or caudal regression syndrome) were observed among more than 1,500,000 infants born in Czechoslovakia from 1959-1966. Five of the 9 mothers involved had been exposed to fat solvents (xylene in 1 case) during their pregnancy. Experiments with chick embryos exposed to xylene atmosphere (a rectangular window was opened in the egg shell then covered with a glass square on a paraffin frame) for 60, 120, 180 or 240 minutes resulted in a significant increase in the incidence of malformations and in the mortality rate in the embryos exposed at the earliest stage of development

Abstracts of two Russian articles (11, 13) state that xylenes exerted a "significant embryotoxic effect" (dose up to 400 mg/kg/day) and a "minor embryotoxic influence" (dose unspecified). No mention of fetal abnormalities was made in either abstract.

Xylenes have been found to cross the placenta in humans (14).

2.8 Metabolism

In vivo, xylene isomers are oxidized to *o*-, *m*-, and *p*-toluic acids, of which the *m*- and *p*-isomers conjugate with glycine and are excreted in the urine as the corresponding toluylglycines, i.e., as *m*- and *p*-methylhippuric acid. *o*-Toluic acid, however, is thought to be excreted as the ether glucuronide (15). In addition, hydroxylation also takes place in the various xylene isomers to produce xylenols which are then excreted as glucuronides in substantial amounts and as ester sulfates in small amounts (16). Unchanged xylenes are not detected in the urine but their elimination via the lungs is a primary excretory route (6).

In rabbits, the three xylene isomers gave 60, 81, and 88% of *o*-, *m*-, *p*-toluic acid, respectively. The resulting *o*-toluic acid was excreted mainly in the unconjugated form or as an ester glucuronide (30% of the dose), but a small amount (0.3% by isolation) is conjugated. There is evidence of hydroxylation of all three isomers; 6 and 4% of the doses of *o*- and *m*-xylene, respectively, are excreted as ethereal sulphate and 10-15% of *o*-xylene is probably excreted as an ether glucuronide (18).

Small amounts of phenolic metabolites have been isolated in the urine of rats, rabbits and guinea pigs given all three isomers orally (35).

Urinary excretion of *m*-, or *p*-methylhippuric acid in the urine of persons exposed to vapors of *m*- or *p*-xylene has been determined by Ogata *et al*. (19) in male volunteers.

Bacterial metabolism of *p*- and *m*-xylene has been reported by Gibson *et al*. (20) *Pseudomonas putida* 39/D oxidized *p*-xylene to *cis*-3,6-dimethyl-3, 5-cyclohexadiene-1,2-diol (*cis*-*p*-xylene dihydrodiol). This metabolite was stable enough to be isolated in crystalline form. In the case of *m*-xylene, *P*. *putida* 39/D oxidized it to 3,5-dimethyl-3,5-cyclohexadiene-1,2 diol. This product was very unstable and all attempts to isolate it led to the formation of 2,4-dimethylphenol.

A metabolic study by Jamison *et al*. (21) was also cited in ref. 20. In this study a strain (V-49) of *Nocardia corallina*, in addition to oxidizing *p*-xylene to *p*-toluic acid and 2,3-dihydroxy-*p*-toluic acid also produced 3,6-dimethyl pyrocatechol and α,α'-dimethyl-*cis*,*cis*-muconic acid. The pathways proposed for the oxidation of *p*-xylene by *N*. *corallina* V-49 and by *P*. *putida* are shown in Figures 4 and 5, respectively.

Gibson *et al*. have reported that rat liver microsomes oxidize *p*-xylene to 3,6-dimethylphenol and *p*-toluic acid whereas *m*-xylene is oxidized predominantly to 2,4-dimethylphenol and a trace of 2,6-dimethylphenol (20).

The absorption of liquid xylene through the skin in man was investigated under experimental conditions (22). It was established that the rate of absorption of liquid xylene was from 4.5 to 9.6 mg/cm^2/hour.

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FIGURE 4. Proposed Pathway for the Oxidation of p-Xylene to ∝, ∝'-dimethylmuconic acid by N. Corallina V-49 (21)

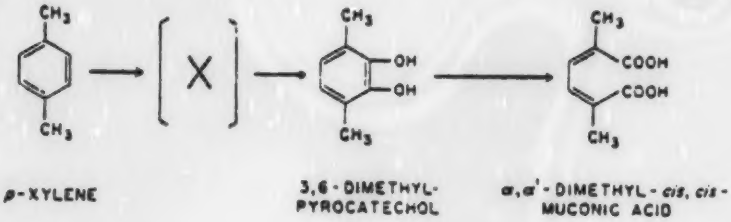
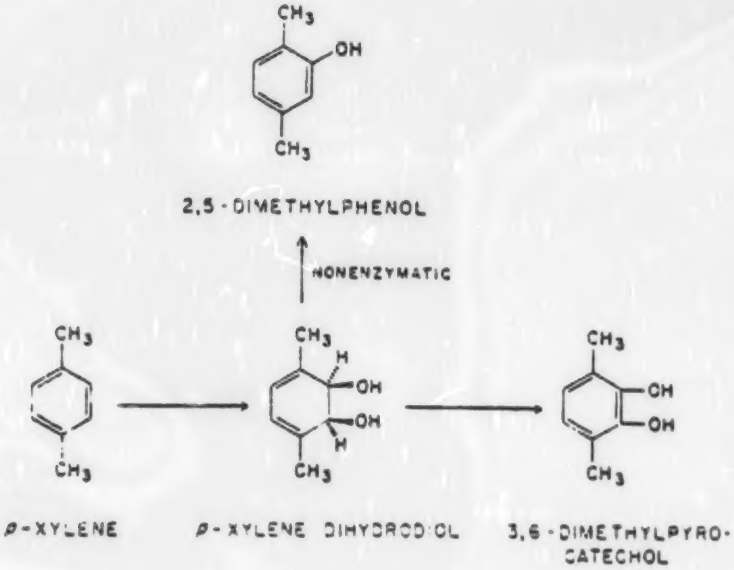

CH_3
CH_3
X
CH_3
OH
OH
CH_3
CH_3
COOH
COOH
CH_3
p-XYLENE
3,6-DIMETHYL-PYROCATECHOL
α,α'-DIMETHYL-cis, cis-MUCONIC ACID

FIGURE 5. Pathway Proposed for the Oxidation of p-Xylene by P. putida (21)


CH_3
OH
CH_3
2,5-DIMETHYLPHENOL
NONENZYMATIC
CH_3
CH_3
CH_3
H
OH
OH
H
CH_3
CH_3
OH
OH
CH_3
p-XYLENE
p-XYLENE DIHYDRODIOL
3,6-DIMETHYLPYRO-CATECHOL

2.9 Ecological Effects

Xylene has caused tainting in scallops (23) and fish (24). In fish muscle, offensive flavors were detectable at concentrations of xylene as low as 0.02 ppm, concentrations similar to those found in fish from a polluted river (4).

The Aquatic Toxicity Ratings (96-hour TLm, species unspecified) for xylene, o-xylene, and p-xylene, are reported to be in the range of 100-10 ppm (G16). The 96-hour LC50 for goldfish is 17 ppm (25). Rainbow trout detect and avoid xylene at concentrations as low as 10 mg/l (26).

At a concentration of 0.2%, xylene inhibited spore germination of marine algae (*Enteromorpha* and *Ectocarpus* spp.) (27). However, at low concentrations in water, xylene stimulated growth of phytoplankton (28).

Xylene was not injurious to pollen of petunias when applied at concentrations similar to those of a pesticide solvent (29).

2.10 Current Testing

Xylenes have been tentatively selected by NCI for carcinogenicity testing (G12).

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APPENDIX B

KEY TO ABBREVIATIONS

TCLo - Lowest published toxic concentration
- the concentration of a substance in air which has been reported to produce any toxic effect in animals or humans over any given exposure time.

TDLo - Lowest published toxic dose
- the lowest dose of a substance introduced by any route other than inhalation over any given period of time that has been reported to produce any toxic effect in animals or humans.

LCLo - Lowest published lethal concentration
- the lowest concentration of a substance, other than an LC50, in air that has been reported to have caused death in humans or animals over any given exposure time.

LDLo - Lowest published lethal dose
- the lowest dose of a substance other than LD50 introduced by any route other than inhalation over any given period of time that has been reported to have caused death in humans or animals.

LC50 - Median lethal concentration
- the concentration of a test material that kills 50 per cent of an experimental animal population within a given time period.

LD50 - Median lethal dose
- the dose of a test material, introduced by any route other than inhalation, that kills 50 percent of an experimental animal population within a given time period.

LT50 - Median Lethal Response Time
-Statistical estimate of the time from dosage to the death of 50 percent of the organisms in the population subjected to a toxicant under specified conditions.

TLm - Median tolerance limit
- the concentration of a test material at which 50 per cent of an experimental animal population are able to survive for a specified time period.

TLV® - Threshold limit value
- the airborne concentration of a substance to which nearly all workers may be repeatedly exposed day after day without adverse effect.

TLV®-TWA - Threshold limit value - time weighted average
- the time-weighted average concentration of a substance for an 8-hour workday or 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

TLV®-STEL- Threshold limit value - short term exposure limit-
- the maximal concentration of a substance to which workers can be exposed for up to 15 minutes without suffering acute or chronic toxic effects. No more than four excursions per day are permitted. There must be at least 60 minutes between exposure periods. The daily TLV-TWA must not be exceeded.

BOD - Biochemical oxygen demand
- a measure of the presence of organic materials which will be oxidized biologically in bodies of water.

NOHS Occupational Exposure:

- Rank
  - an ordering of the approximately 7000 hazards occurring in the workplace from most common to least common

- Estimated number of persons exposed
  - includes full- and part-time workers. For hazards ranked 1 through 200, the figure projected to national statistics by NIOSH is given; for the remaining hazards the number of people exposed given in the survey was multiplied by a fixed number to give a rough estimate of national exposure. The fixed number used, --30--, is derived from the statistical sampling technique used in this survey.

i - insoluble

ss - slightly soluble

s - soluble

vs - very soluble

∞ - soluble in all proportions

bz - benzene

chl - chloroform

eth - ether
peth - petroleum ether
ace - acetone
lig - ligroin
alc - alcohol
CCl_4 - carbon tetrachloride
dil. alk. - dilute alkalis
CS_2 - carbon disulfide
os - organic solvents
oos - ordinary organic solvents